Rajendra A. Badwe · Sudeep Gupta ·
Shailesh V. Shrikhande · Siddhartha Laskar
Editors

Tata Memorial Centre Textbook of Oncology

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The *TMC Textbook of Oncology* is dedicated to…

…. the countless patients who visit Tata Memorial Centre bestowing their faith upon this institution in their darkest hours. They are our *raison d'être!* We are grateful to them for their inspiration to work harder towards ever higher levels of clinical excellence...

… the trainee doctors, the heartbeat of our hospitals, whose hard work and commitment to service and education make TMC a great institution…

… the nursing staff whose unwavering commitment and profound dedication to patient care embody the heart and soul of our institution…

… to the paramedical staff of TMC, whose skills and dedication are indispensable to the care we provide…

… to colleagues from the departments of general and hospital administration, accounts, purchase, engineering, and all other supportive teams operating seamlessly in the background, who are the pillars that enable the smooth and efficient functioning of our institution…

… medical social workers who provide practical assistance, addressing vital aspects of patient care…

… to the workforce members of TMC, including housekeeping and other staff, whose work is often unseen, yet indispensable, and is the backbone of patient care...
… to the volunteers and Non-Governmental Organizations (NGOs) that collaborate with TMC and offer invaluable support to our patients…

Preface

It is with immense pride and a deep sense of responsibility that we present the *Tata Memorial Centre Textbook of Oncology.* This comprehensive volume, a collaborative effort led by faculty member colleagues of Tata Memorial Centre (TMC), along with contributions from TMC alumni, is more than just a textbook. It is a testament to the spirit of multidisciplinary oncology practice at TMC.

Our journey in creating the *Textbook of Oncology* was inspired by the diverse and complex landscape of cancer care in India. As a nation with vast demographic and geographic diversity, the challenges in cancer care are as unique as they are formidable. Recognizing this, our aim was to provide a resource that is not only academically rigorous but also deeply rooted in the practical realities of local practice. It offers an authentic overview of the TMC approach to multidisciplinary cancer care, with insights that, we hope, will be valuable both within and beyond India.

In presenting the *Textbook of Oncology*, our objective is twofold: to provide a comprehensive resource that contextualizes the practice of oncology in TMC and to offer insights into delivering high-quality cancer care in diverse global settings. Our focus has been on the practical application of oncological principles within Indian and similar healthcare systems. However, oncologists and healthcare professionals from developed countries will also find this resource enlightening, providing a broader perspective on how quality cancer care can be delivered in different parts of the world.

The *Textbook* is designed to cater to a wide array of readers—from undergraduate medical students to postgraduates specializing in general surgery, general medicine, paediatrics, gynaecology, radiation oncology, and other disciplines. A notable feature of the *Textbook* is its utility in preparing students for entrance and exit examinations. However, the content is not just theoretical; it is enriched with practical insights, thus preparing students for the practical aspects of cancer care. To the community of practising oncologists, it will serve as a reliable and up-to-date reference that encapsulates the essence of contemporary oncology practice.

As editors, two of us being surgical oncologists, one a medical oncologist, and another a radiation oncologist, we have witnessed firsthand the evolution of cancer diagnosis and treatment. Our collective experiences have taught us that cancer care is an ever-changing landscape requiring continuous learning and adaptation. The *Textbook*, therefore, not only covers the specifics of various cancers but also delves into broader themes such as cancer epidemiology, genetics, principles of systemic therapy, oncology-related training and education, and others. The chapters are structured to facilitate easy understanding and retention of complex concepts, making it an ideal study aid.

We extend our gratitude to all the authors who have contributed their knowledge and experience. Their dedication and expertise have been instrumental in shaping this work. We also wish to thank our publisher, Springer, for their collaboration and support in bringing this project to fruition. A special acknowledgement goes to the staff, particularly Mr Yogesh Kembhavi, the Editorial Assistant, whose diligent efforts and commitment have been crucial in the successful compilation and publication of the Textbook.

We are mindful of the profound influence that a great textbook can have on its readers. Throughout the history of medical education, certain texts have transcended their basic role as educational resources, becoming lifelong companions. Through this inaugural edition of the *TMC Textbook of Oncology*, we hope to sow the seeds of a work that will make its place as a trusted companion in the minds of its readers, to be consulted and cherished throughout their professional lives.

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Part I

Basic Principles

Basic and Translational Science in Oncology

Dimple R. Bhatia and Sudeep Gupta

Abbreviations

APC/C	Anaphase-promoting complex/cyclosome
APE	Apurinic/apyrimidinic (AP) endonuclease
APML	Acute promyelocytic leukemia
ATM	Ataxia-telangiectasia mutated kinase
ATRA	All-*trans* retinoic acid
BER	Base excision repair
CAR	Chimeric antigen receptor
CCNE1	Cyclin E1
CCNE2	Cyclin E2
CDKi	Cyclin-dependent kinase (CDK) inhibitor
CENP-C	Centromere protein C
CHK1	Checkpoint kinase 1
CML	Chronic myelogenous leukemia
DBD	DNA-binding domain
DDR	DNA damage repair
DNA-PK	DNA-dependent protein kinase
DNMT	DNA methyltransferase
DSBs	Double-strand breaks
E2F-DP	E2 promoter binding factor-dimerization partner
ECs	Endothelial cells
EGF	Epidermal growth factor
FAK	Focal adhesion kinase
HDAC	Histone deacetylase
HGF	Hepatocyte growth factor
HIC-1	Hypermethylated in cancer
HR	Homologous recombination
ICAM1	Intercellular adhesion molecule 1
JAK	Janus-activated kinase
KAI-1	Kangai-1
LOH	Loss of heterozygosity
MMP	Matrix metalloproteinase
MQ	Methylene quinuclidinone
NER	Nucleotide excision repair
NHEJ	Non-homologous end joining
PARP	Poly (ADP-ribose) polymerase
PCNA	Proliferating cell nuclear antigen
PHTS	Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) hamartoma tumor syndrome
PLK1	Polo-like kinase 1
polβ	Polymerase-β
PPARγ	Peroxisome proliferator-activated receptor-gamma
PTEN	Phosphatase and tensin homologue deleted on chromosome 10 (PTEN)
RANKL	Receptor activator of nuclear factor kappa B (NF-κB) ligand
Rb	Retinoblastoma
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
SAC	Spindle assembly checkpoint
SDF1	Stromal cell-derived factor 1
SSB	Single-strand break
STK	Serine/threonine kinase
TAM	Tumor-associated macrophage
TCR	T-cell receptor
TGF-β	Transforming growth factor-β
TME	Tumor microenvironment
VCAM1	Vascular cell adhesion molecule 1
WT	Wild-type

1 Introduction

Cancer ranks amongst the top five leading causes of death worldwide. According to recently published data, an estimated 18.1 million new cancer cases and 9.6 million cancer deaths had occurred in 2018 [1]. Although the incidence of

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cancers is lower in developing regions of the world, they account for a majority of the cancer burden because of their population size. In India, there were an estimated 1.15 million new cases and 0.78 million deaths in 2018 [1]. Furthermore, the burden of cases and deaths is expected to increase in the coming decades because of a variety of reasons, most important among which is the likely aging of the world's population. This picture positions translational cancer research as one of the top health research priorities worldwide. A comprehensive understanding of the tumor biology and the pathophysiological processes that govern cancer onset and spread is required for the development of detection techniques, diagnostic and prognostic biomarkers, novel therapies, and cancer prevention strategies. Innovative research to address these key areas of development is helped by continuous mining and analysis of the so-called "omics" data obtained through advancements in technology. In this chapter, we describe the outcome of research in some of the most important themes in cancer, namely, tumor cell biology, hallmarks of cancer, DNA repair mechanisms, regulation of gene expression, functions of oncogenes and tumor suppressors, and the role of the immune system in regulation of cancer initiation and spread.

2 Hallmarks of Cancer

"Hallmarks of cancer" is a term coined by Hanahan and Weinberg to summarize the principal characteristics of malignant cells and their possible underlying molecular underpinnings, which they reported in two famous papers [2, 3]. The "hallmarks of cancer" framework provides a set of 10 major principles that encompass the complexity of cancer biology. By definition, these hallmarks are "distinctive and complementary capabilities" that enable tumor growth and metastatic dissemination [2, 3]. A summary of these hallmarks is listed in Table 1. Of these, the six acquired capabilities—self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis, limitless replicative

Table 1 Cancer hallmarks [2, 3]

Hallmark	Pathogenicity	Mechanism	Therapeutic targeting of hallmarks (examples)
Acquired capability: self-sufficiency in growth signals	Uncontrolled growth and cell division	Oncogene addiction/signaling, signaling between different cell types in the heterogeneous tumor	EGFR inhibitors
Acquired capability: insensitivity to anti-growth signals	Unchecked proliferation	Switch off of the cell cycle checkpoints, avoiding cytostatic anti-growth signals	CDKis
Acquired capability: evading apoptosis	Evading cell attrition	Inactivation of tumor suppressors like pRb, p53, etc.	Inhibitors to rescue mutant p53 conformation and function to restore wild-type p53 activity
Acquired capability: limitless replicative potential	Increased proliferation; avoiding senescence	Inactivation of tumor suppressors like pRb and p53; telomere maintenance through upregulation of telomerase	p53 peptidomimetics
Acquired capability: sustained angiogenesis	Continuous supply of nutrients through an increased vasculature	Changing the balance of angiogenesis inducers like VEGFR, fibroblast growth factor receptor (FGFR), etc., increase in integrin signaling, and reprogramming to alter cytokine balance	VEGFR inhibitors
Acquired capability: tissue invasion and metastasis	Escape the primary tumor mass and colonize a new terrain in the body where, at least initially, nutrients and space are not limiting	Alteration of cell–cell adherence molecules like cadherins and integrins, upregulation of MMPs, cytokines	HGF/cellular mesenchymal epithelial transition factor (c-MET) inhibitors
An enabling characteristic: genomic instability and mutation	Facilitation of all hallmarks	Random mutations, including chromosomal rearrangements; translocations, loss of heterozygosity, copy number alterations, etc.	PARP inhibitors in BRCA-deficient tumors
An enabling characteristic: tumor-promoting inflammation	Aids in tumor cells' acquired abilities of proliferation, invasion, and metastasis	Alteration of the TME and tumor stromal interactions, enabling proliferation, invasion, and metastasis	Selective anti-inflammatory drugs
An emerging hallmark: reprogramming energy metabolism	Support continuous cell growth and proliferation	Replacing the metabolic program that operates in most normal tissues and fuels the physiological operations of the associated cells; Warburg effect	Aerobic glycolysis inhibitors
An emerging hallmark: evading immune destruction	Active evasion by cancer cells from attacks and elimination by immune cells	Cancer cells may paralyze infiltrating CTLs and NK cells, by secreting TGF-β or other immunosuppressive factors; recruitment of inflammatory cells that are actively immunosuppressive, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs)	Immune checkpoint inhibitors anti CTLA-4 or PD-1/PDL-1 antibodies

potential, sustained angiogenesis, and invasion and metastasis—are shared in common by most and perhaps all types of human cancers. The two enabling characteristics, viz., genomic instability and inflammation, are crucial to the acquisition of the six hallmark capabilities and to two new "emerging hallmark" capabilities that include reprogramming energy metabolism and evading immune destruction. The latter involves the interaction of tumor cells with the tumor microenvironment (TME) to influence its constitution and signaling interactions with the surrounding stromal cells. These suggested hallmarks and capabilities of cancers were sought for their systematic use in designing effective treatments in the last decade. The major biological mechanisms that aid in the acquired, enabling, and emerging tumor hallmarks include oncogene addiction, inactivation of tumor suppressors, abnormal regulation of gene expression, escape from cell cycle checkpoints, deregulated DNA damage and repair, immune destruction, metabolic reprogramming, and acquisition of invasive and metastatic abilities. An interplay of all these mechanisms along with their contribution to developing effective treatment modalities in cancer is discussed in the subsequent sections.

3 Biological Underpinnings of the Cancer Hallmarks

3.1 Oncogenes and Tumor Suppressor Genes

In an extremely fundamental sense, cancer is a genetic disease. Two types of genetic mutations, namely, gain of function in oncogenes (oncogene addiction) and loss of function in tumor suppressor genes (TSGs), form important molecular bases of carcinogenesis, mainly through downstream effects on cell proliferation and avoidance of programmed cell death (apoptosis). Additionally, through highly interconnected signaling networks, these genes regulate multiple hallmarks of cancer.

3.1.1 Oncogene Addiction/Aberrant Cell Signaling

The term "oncogene addiction" was first coined by Dr. Bernard Weinstein to describe the reliance of tumor cells on a specific oncogenic protein or oncogenic pathway for their proliferation, survival, and malignancy [4]. Designation of "oncogene" is assigned to a specific set of genes after several preclinical and clinical "proof-of-concept" validation studies. Identification of oncogenes and their mechanistic studies has helped develop novel and effective therapies that target and restrict both tumor growth and spread [5]. Oncogene addiction is primarily characterized by abnormal production of growth-promoting signals that regulate the entry and progression of cells through the cell growth and division cycle that is otherwise strictly regulated in normal tissue cells. This leads to a loss of cell homeostasis, normal tissue architecture, and function. Oncogenic signals are generally conveyed through kinases that act as major signal transducers governing a variety of cellular activities such as metabolism, transcription, cell cycle progression, cytoskeletal rearrangement and cell movement, apoptosis, and differentiation. A major fraction of the oncogenic drivers is comprised of receptor kinases that include receptor tyrosine kinases (RTKs) like endothelial growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), etc. and serine/threonine kinases (STKs) like phosphoinositide 3-kinase (PI3K), mammalian target of rapamycin (mTOR), etc. Non-receptor tyrosine kinases that act as signal transducers include c-Abl, Src, Janus-activated kinases (JAKs), focal adhesion kinases (FAKs), etc. Whilst RTKs are activated through extracellular mitogenic signals, non-receptor tyrosine kinases, located both in the cytosol and nucleus, are activated by intracellular signals [6, 7]. Mutations and dysregulation of oncogenic protein kinases are implicated in the development and progression of various cancers. The mechanisms of aberrant oncogenic signaling in cancer cells include overexpression of receptors or their cognate ligands, gene amplification, mutations, chromosomal rearrangements, and autocrine (expression of growth factor ligands) and paracrine (relay of signals through tumor-associated stroma) signaling [8, 9].

A good clinical example of oncogene addiction is chronic myelogenous leukemia (CML). CML is driven by the Bcr-Abl mutant oncogene, produced as a result of chromosome 9:22 translocation (Philadelphia chromosome). Addiction of CML to Bcr-Abl was demonstrated by the clinical success of the Bcr-Abl kinase inhibitor imatinib in CML patients [10]. This success proved the proof of concept of the effectiveness of molecular targeting, thus giving a thrust to the translational research in the area of oncogene addiction. This subsequently led to the emergence of several targeted anticancer therapies based on the study of oncogene addiction. Several successful drugs have emerged in the last two decades based on oncogene addiction: RTK inhibitors like erlotinib (EGFR), bevacizumab (VEGFR), trastuzumab [human epidermal growth factor receptor 2 (HER2)], crizotinib [anaplastic lymphoma kinase (ALK)], etc.; STK inhibitors like everolimus (mTOR), vemurafenib (B-RAF), etc.; and non-receptor kinase inhibitors like imatinib (Bcr-Abl), tofacitinib (JAK), etc. Molecular medicine based on oncogene addiction is now an accepted norm in cancer treatment and has been highly successful in several cancers. A few examples based on clinical success through oncogenic targeting is listed in Table 2.

Table 2 Examples of RTK-targeted molecular cancer therapies

Inhibitor	Target	Approved for
Trastuzumab (Herceptin)	HER2	HER2-positive breast cancer
Cetuximab (Erbitux) Panitumumab (Vectibix)	EGFR	Metastatic colorectal cancer (RAS wild-type) Metastatic non-small cell lung carcinoma (NSCLC)
Gefitinib (Iressa) Erlotinib (Tarceva)	EGFR	Metastatic colorectal cancer (RAS wild-type) Metastatic NSCLC
Lapatinib (Tykerb)	EGFR and HER2	HER2-positive breast cancer (Trastuzumab-resistant)
Bevacizumab (Avastin)	VEGFR	Metastatic colorectal cancer (mCRC)

3.1.2 Tumor Suppressors

Tumor suppressor genes are defined as a set of genes whose loss of function results in the promotion of tumor growth and malignancy. The products of TSGs classified as tumor suppressor proteins negatively regulate cell growth or promote cell death, thus restricting the potential for tumor formation. Thus, inactivation of tumor suppressor genes through genetic alterations or dysregulation can lead to unregulated cell growth and tumor development. Most tumor suppressor genes follow the characteristic “two-hit” hypothesis proposed by Alfred Knudson, which states that both gene alleles must be lost to unmask the malignant phenotype [11]. Mutations or loss of heterozygosity (LOH) are the most common molecular alterations in tumor suppressor genes, leading to loss of tumor suppressor activity. In addition to these, tumor suppressor genes can be functionally inactivated through epigenetic modulation (e.g., methylation) of the gene promoter that causes its transcription, proteasome-mediated degradation, or aberrant interacting proteins [12]. The most commonly encountered aberrant tumor suppressor genes in cancers include the cell cycle regulatory protein retinoblastoma (Rb) susceptibility gene, p53, breast cancer susceptibility genes (BRCA 1 and 2), and phosphatase and tensin homologue deleted on chromosome 10 (PTEN).

Retinoblastoma (Rb) Suppressors

The Rb or retinoblastoma susceptibility gene was the first tumor suppressor gene to be identified and characterized. Retinoblastoma is a rare childhood eye tumor. It can be either familial (hereditary) or sporadic (nonhereditary) [13]. The Rb protein is encoded by the RB1 gene located on chromosome 13 (13q14.1–q14.2 locus). It is a universal cell cycle regulator with a central role in governing the passage of cells through the G1 phase as described in the section “The cyclin–CDK–Rb Axis.” Rb binds and inhibits E2 promoter binding factor–dimerization partner (E2F–DP) dimers. E2Fs are transcription factors (TFs) that regulate genes involved in G1–S- and S-phase progression of the cell cycle [cyclin E, cyclin A, proliferating cell nuclear antigen (PCNA)]. By keeping E2F–DP inactivated, RB1 restricts the cell in the G1 phase, acting as a growth suppressor, and, hence, is also referred to as “the restriction point of cell cycle control” [14]. The Rb–E2F–DP complex also attracts a histone deacetylase (HDAC) protein to the chromatin, reducing transcription of the S phase-promoting factors, further suppressing DNA synthesis. In addition to its role in restricting cell cycle progression in association with the E2F transcription factor, Rb can regulate senescence, chromosomal segregation, checkpoint controls, apoptosis, and terminal differentiation of cells through posttranslational modifications (acetylation, methylation, etc.) [15–18]. The most common strategy applied in translational research for restoration of Rb suppressor function is maintenance of the E2F–Rb complex. In this direction, several cyclin-dependent kinase inhibitors (CDKi) (flavopiridol, palbociclib, ribociclib, roscovitine, etc.) have been designed and are at different phases of clinical trials or are approved for use, as listed in Table 5. Similarly, Rb deficiency is linked to overexpression of the G2–M checkpoints. Hence, targeting CHK1, polo-like kinase 1 (PLK1), etc. may abrogate the downstream pathways of cell cycle progression and prove beneficial in treating Rb-deficient tumors [19].

The p53 Gene

The tumor suppressor p53 is a pivotal protein in the maintenance of genomic integrity. It is appropriately called the “guardian of the genome” [20]. This protein is encoded by the TP53 gene located on chromosome 17 (17p13.1 locus). In addition to the full-length protein, at least 12 protein isoforms (p53 isoforms), ranging in size from 3.5 to 43.7 kDa, are encoded by the human TP53 gene [21]. p63 and p73 are other tumor suppressor proteins belonging to the p53 family. These proteins are involved in cellular responses to stress and development and share significant structural and functional homologies with p53, particularly in the DNA-binding domain (DBD) [22, 23]. p53 is the most commonly mutated gene in cancer with mutations detected in approximately 50% of all human cancers [20]. Germline p53 mutations are associated with Li–Fraumeni syndrome, a hereditary predisposition linked to several cancers [24]. The biological role of p53 is primarily attributed to its activity as a transcription factor, with most pathogenic p53 mutations being found in the DNA-binding domain (DBD) of the protein. Other p53 mutations largely influence its nuclear localization, oligomerization, and transactivation functions [25, 26].

Under normal conditions, p53 has an extremely short half-life (approximately 20 min) and a low steady-state protein level. It is maintained in an inactive state by binding to its negative regulator protein, the mouse double minute 2 (MDM2) ligase. In response to DNA damage or other cellular stress signals (e.g., nutrient deprivation, hypoxia, etc.), p53 is stabilized through inactivation of MDM2 to perform its tumor suppressor role [26]. Activated p53 acts as a transcription factor transcribing a number of genes, including the CDKi p21. It causes arrest of the cell cycle in the G1 or G2 phase to allow for DNA repair, as shown in Fig. 1. It can also contribute to DNA damage repair by activating genes that facilitate single-strand breaks (SSBs) of repair pathways [nucleotide excision repair (NER) and base excision repair (BER)] through its interaction with apurinic/apyrimidinic (AP) endonuclease (APE) and DNA polymerase-β (polβ) [28, 29]. In response to severe DNA damage, p53 functions to redirect the cell into a permanent cell cycle arrest, senescence, and apoptosis. Additionally, p53 is also implicated in the regulation of angiogenesis and metastasis. p53-regulated angiogenesis and metastasis regulators include the tumor suppressor protein maspin, hypermethylated in cancer (HIC-1) proteins, and the metastasis suppressor protein Kangai-1 (KAI-1) [30–32]. Other functions of p53 include regulation of glycolysis and reactive oxygen species (ROS) that contribute to its tumor suppression effect by influencing the emerging hallmarks of cancer, viz., metabolism and tumor–tumor microenvironment (TME) interaction, respectively [33]. p53 is also capable of interacting with other cellular pathways [e.g., PI3K, B-cell lymphoma 2 (BCL-2), survivin, myeloid cell leukemia-1 (MCL-1), insulin-like growth factor (IGFR), etc.] to trigger apoptosis or cellular differentiation [34]. Due to its pleiotropic role in the regulation of numerous cellular functions, various strategies have been used to restore its tumor suppressor functions. In this direction, gene therapy and supplementation with the p53 peptide strategy has resulted in a phase II clinical trial with a p53 peptide vaccine with or without interleukin-2 (IL-2) (NCI-99-C-0138) and in a phase II study of Ad5CMV-p53 gene therapy (INGN 201) plus docetaxel [35]. Other strategies that can be employed to effectively restore p53 functions include activation and restoration of wild-type (WT) p53, reactivation of p53 activity through conformational changes in the mutant p53 structure, depletion of mutant p53, targeting of proteins that negatively interact with p53, bypassing the requirement for upstream p53 activation [Bcl-2 homology 3 (BH3) mimetics, e.g., ABT-737], synthetic lethality approach with cell cycle regulatory proteins like CHK1, WEE1, PLK, etc., and inhibition of pathways activated downstream of mutant p53 [35, 36]. Pharmacological targeting has shown success in preclinical studies, and several inhibitors have entered into clinical trials. APR-246 is a first-in-class agent targeting mutant p53, leading to reexpression of wild-type p53 activity. It has shown efficacy against a broad range of p53 mutations (ClinicalTrials.gov identifier: NCT03745716). It is a prodrug that gets metabolized to methylene quinuclidinone (MQ), which acts as the active drug. MQ acts by covalently linking the thiol groups on cysteine residues in the p53 core domain. This results in a conformational change in the p53 protein, leading to restoration of its tumor suppressor function. Similarly, COTI-2 is an orally bioavailable compound that restores p53 tumor suppressor function by inducing conformational changes in the mutant p53. It is a Food and Drug Administration (FDA)-designated orphan drug for treatment of ovarian cancer (http://cotingapharma.com/pipeline/coti-2/). WR1065, a derivative of the radioprotectant drug amifostine activates p53 through a DNA damage-independent and redox-dependent mechanism [37]. Similarly, repositioning of several compounds [arsenic trioxide, statins, histone deacetylase (HDAC) inhibitors, etc.], which can block p53 oncogenic activity by depletion of p53 mutant function, is being investigated [35, 36]. Another strategy that has shown promise in preclinical studies involves prevention of premature termination of TP53-messenger RNA (mRNA) translation, resulting from nonsense mutations. This involves use of high concentrations of aminoglycosides that can restore gene function by allowing premature termination codon read-through and thus restoring active proteins resulting from genetic defects caused by nonsense mutations. CDX5–1 is an example of one such compound that specifically restores p53 functional protein when used in combination with aminoglycosides [38]. A summary of strategies targeting p53 is provided in Table 3 [35–38].

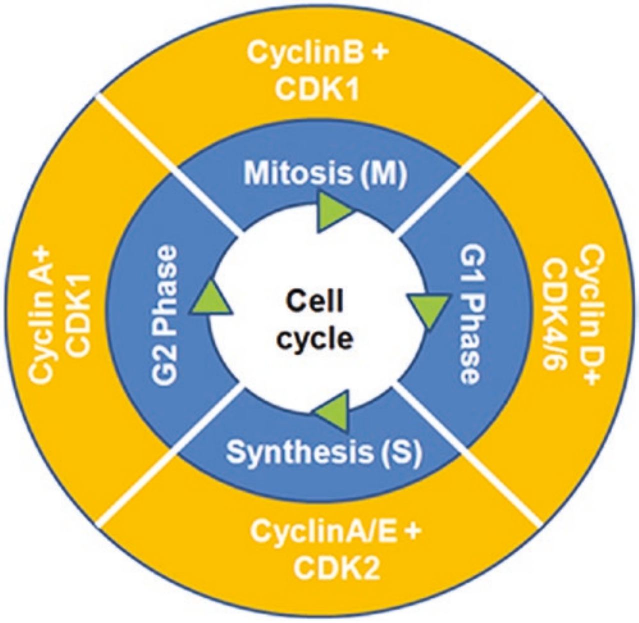

Fig. 1 Regulation of cell cycle phases by cyclin/CDK regulatory proteins [27]

Breast Cancer Susceptibility Genes: BRCA1 and BRCA2

In the 1990s, BRCA1 and BRCA2 were discovered in Mary-Claire King's Laboratory at UC Berkeley and subsequently characterized as breast cancer susceptibility genes predis-

Table 3 Strategies targeted at restoration of p53 function [35–38]

Strategy	Compounds	Clinical trial status
Wild-type p53 restoration and activation	MDM2 inhibitors (idasanutlin, benzodiazepinone)	Idasanutlin, phase 1 (NCT03362723)
p53 peptides for restoration of p53 levels	Modified vaccinia virus Ankara expressing p53	Phase 1 (NCT02275039)
p53 gene therapy for restoration of p53 levels	Adenoviral human p53 gene (rAd-p53)	Phase 2 (NCT02561546)
p53 synthetic long peptide vaccine	p53-SLP vaccine	Phase 2 (NCT00844506)
Dendritic cell-based p53 vaccine	Ad.-p53 DC	Phase 2 (NCT03406715)
Pharmacological inhibitors to rescue mutant p53 conformation and function to restore wild-type p53 activity	PRIMA-1MET (APR-246)	Phase 1 (NCT03072043, NCT02999893)
	WR-1065 or RadProtect®	Phase I (NCT02587442)
	COTI-2	Phase I (NCT02433626)
Depletion of mutant p53	Arsenic trioxide Approved for acute promyelocytic leukemia (APL)	Phase 2 (NCT01428128)
	SAHA (histone deacetylase (HDAC) inhibitor) Approved for the treatment of cutaneous T-cell lymphoma	Phase 1 (NCT02042989) phase 2 (NCT00121225)
	Disulfiram (DSF)	Phase 1 (NCT01907165)
	Heat shock protein (HSP) 90 inhibitors (geldanamycin)	Phase 2 (NCT00093405)
Alteration of proteins that interact with, stabilize, and/or contribute to the oncogenic activity of mutant p53	All-*trans* retinoic acid (ATRA)	FDA-approved for the treatment of APML
Inhibiting pathways activated downstream of mutant p53	Statins, metformin	Approved drugs for repositioning in cancer treatment
	Sunitinib, PARP inhibitors, proteasome inhibitors	Approved drugs
Synthetic lethality approaches	UCN-01 (CHK1 inhibitor)	Phase 2 (NCT00045747)
Targeting the downstream pathways of mutant p53	WEE1 inhibitors (such as PD0166285 and AZD1775)	Phase 1 (NCT02906059) and phase 2 (NCT02593019)
	BI-2536 (and other polo-like kinase 1 (PLK1) inhibitors)	Phase 1 (NCT02211872) and phase 2 (NCT00706498)
Preventing premature termination of TP53-mRNA translation owing to nonsense mutations	CDX5–1 plus aminoglycoside antibiotics	Preclinical

posing carriers to breast, ovarian, and other cancers. The BRCA1 gene is located on chromosome 17 locus 17q21, whereas BRCA2 is located on chromosome 13 locus 13q12. The BRCA1 or BRCA2 mutation carriers have a lifetime breast cancer risk of 50–80% and a lifetime ovarian cancer risk of 10–20% [39, 40]. These genes are referred to as "caretakers" of the human genome since deficient cells tend to accumulate DNA damage, leading to oncogenesis. These lesions include chromosomal breaks, aberrant mitotic exchanges, and abnormal DNA ploidy [41].

BRCA1 is a nuclear phosphoprotein and an essential component of the cellular DNA damage repair (DDR) machinery. It binds to the DDR sensor Mre11, Rad50, Nbs1 (MRN) complex and guides the localization of the recombinase RAD51 to the damaged DNA foci to mediate DDR in response to double-strand breaks (DSBs) [42–44]. Similar to BRCA1, BRCA2 is also a nuclear phosphoprotein that binds to RAD51 and MRE11 to regulate DSB repair and maintain chromosomal integrity [44]. Homologous recombination (HR) and Non-homologous end joining (NHEJ) are the two major mechanisms of DSB repair in mammalian cells. Non-homologous end joining is an error-prone repair mechanism that does not require a complementary sister chromatid and functions at the G1 phase, whereas the error-free homologous recombination repair occurs by ligation of homologous sister chromatids during the S and G2 phases [45]. BRCA gene products are essential for the homologous recombination repair mechanism. They serve as a scaffold protein to integrate different components of the homologous recombination machinery [replication protein A (RPA), X-ray repair cross-complementing 1 (XRCC1), polβ, etc.] as well as resection of 5′-end of double-strand breaks [46]. In addition to DNA repair, BRCA1 also has important roles in transcriptional regulation, differentiation, and ubiquitination as an E3 ligase [47, 48]. Therapeutically, a deficient homologous recombination repair abnormality has been targeted using a synthetic lethal targeting strategy with poly (ADP-ribose) polymerase (PARP) inhibitors and several PARP inhibitors (olaparib, rucaparib, etc.) are approved in the treatment of ovarian and breast cancers [49].

Phosphatase and Tensin Homologue Deleted on Chromosome 10 (PTEN)

Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) is a tumor suppressor that is mutated or lost in several cancers [50]. The protein is encoded by the PTEN gene on chromosome 10 (locus 10q23). It is a lipid phosphatase that catalytically dephosphorylates phosphatidylinositol-3,4,5-trisphosphate (PIP3), which, in turn, is a potent activator of the AKT kinase in the PI3K–AKT–mTOR pathway. PTEN germline mutations are observed in 60–80% of patients with PTEN hamartoma tumor syndrome (PHTS) or Cowden syndrome [51]. Somatic mutations in PTEN are found in a wide variety of tumors (breast, prostate, glioma, melanoma) [51]. A loss of PTEN function leads to increased expression of the PI3K–AKT pathway, which is the major cellular pathway regulating numerous hallmarks of cancer, including cell proliferation, survival, angiogenesis, metastasis, and metabolism [52]. Numerous cellular functions are regulated by PTEN. It acts as a cell cycle regulator through its ability to reduce cyclin D1 levels and increases CDKi p27 via its lipid phosphatase activity, thus preventing cell cycle progression [53]. Cytoplasmic PTEN is primarily involved in regulating PI3K–AKT signaling, regulation of proliferation, and cellular metabolism, whereas nuclear PTEN regulates chromosomal stability, DNA repair, and apoptosis. Nuclear PTEN is reported to interact with centromere binding protein C (CENP-C), an essential component for centromeric stability, and induces RAD51, which is involved in DNA double-strand break repair [54, 55]. It also binds to the anaphase-promoting complex (APC), thus regulating DNA stability, replication, and repair. The APC/C^{CDH1} (cyclosome) complex is active during mitosis, and its substrates include cyclins (cyclins A and B), kinases (Aurora kinases, PLK1), chromosomal segregation proteins (Securin, SGO1), DNA replication proteins (Geminin, Cdc6), an F-box protein (SKP2), and transcription factors (Ets2, FoxM1) [56].

Therapeutic strategies targeting cancers with loss of PTEN function include targeting the PI3K pathway kinases, namely, the PI3K and mTOR inhibitors. A number of PI3K inhibitors are in clinical trials and include BEZ235, BGT226, etc. Several mTOR inhibitors are approved anticancer drugs and include everolimus, temsirolimus, etc. Due to their role in the maintenance of genomic stability, PTEN-deficient tumors can also be targeted with DNA damage response inhibitors such as PARP inhibitors (olaparib, rucaparib, etc.), PLK, WEE-1, etc. Other therapeutic strategies that have been proposed to target tumors with PTEN loss include use of statins that promote the activity of the transcription factor peroxisome proliferator-activated receptor-gamma (PPARγ), which, in turn, upregulates PTEN mRNA levels and hence its expression. Since PTEN is also rendered inactive through epigenetic modifications like methylation, epigenetic modulators like DNA methyltransferase (DNMT) inhibitors such as azacytidine may restore its expression. In a preclinical study, restoration of the PTEN level was achieved using the mRNA of the PTEN pseudogene PTENP1 to sequester microRNAs (miRNAs) that repress PTEN translation [35, 57, 58].

3.2 Regulation of Gene Expression

Genetic aberration is a common feature of cancer, and random mutations, including chromosomal rearrangements, translocations, loss of heterozygosity (LOH), and copy number alterations, are commonly encountered in oncogenes and tumor suppressors. Normal gene expression is regulated through various epigenetic, transcriptional, posttranscriptional, translation, or posttranslational mechanisms, several of which are found to be altered in cancer. Regulation of gene expression in all cells is primarily mediated at the transcription initiation step. The transcription control center can lie in the promoter (binding site for RNA polymerase II), enhancer, or silencer sequences. Transcription factors (TFs) are proteins or protein complexes that are the final effectors of signal transduction pathways, which transduce the proliferation signals elicited by growth factors. Transcription factors can bind directly to the promoter region of a DNA or RNA polymerase molecule. Chromatin modulation through epigenetic modification is an additional mechanism of gene expression regulation. The switching between inactive and active chromatin mediated by epigenetic events include histone modifications like demethylation and acetylation.

Transcriptional dysregulation in cancer can be a result of disease-defining genetic alterations. These alterations can regulate transcription factors indirectly through mutation of converging signaling factors or directly through genetic alterations in transcription factors or transcriptional machinery components like signaling proteins, cofactors, chromatin regulators, chromosome-structuring proteins, or *cis*-elements (Table 4) [59]. Increasingly, molecular regulators of transcriptional control are being explored as attractive anticancer targets. In this direction, inhibition of an oncogenic transcription factor, promyelocytic leukemia/retinoic acid receptor alpha (PML–RARA), by all-*trans* retinoic acid (ATRA)

Table 4 Components of gene expression regulators dysregulated in cancer [59]

Component	Role	Gene/gene product
Cis-elements	Enhancers	TAL1, LMO2
	Promoters	TERT
	Insulators	TAL1
Transcription factors (TFs)	Master or lineage TF	RUNX1, TAL1, WT1, HOX
	Proliferation TF	MYC, p53
	Signaling TF	STAT3, NOTCH, RAR, AR, ER
Transcriptional coactivators	Mediator complex	MED12
	Cohesin complex	STAG2, SMC3
	Cyclin-dependent kinase	CDK12
Chromatin regulators	Histone writers	EZH2, P300/CBP, MLL1–4, SETD2
	Histone readers	BRD4, TRIM33, ING1
	Histone erasers	JARID1A, UTX
	Chromatin remodelers	SS18
RNA polymerase II		Q403, L438_H439del
Histones		H3K27M, H3K36M, H3K79

has shown clinical benefit as treatment for acute promyelocytic leukemia (APML) [60]. Other strategies for targeting transcription factors and their control machinery include bromodomain-containing protein 4 (BRD4) inhibitors (e.g., JQ1) in NUT midline carcinoma [61, 62], inhibition of CDKs (CDK7, CDK12) that govern RNA pol II activity [63], inhibition of disruptor of telomeric silencing 1-like (DOT1L) histone methyltransferase that controls transcriptional activity by demethylating H3K79 [64], chromatin regulators such as histone demethylases (KDM5A) and histone deacetylases (HDACs) [65], etc.

3.3 Dysregulation of Cell Cycle Checkpoints

Cell cycle regulation is an essential feature in the maintenance of tissue homeostasis. Disruption of the normal cell cycle leads to unchecked cell proliferation, growth, and disturbance of the normal tissue architecture. The cell cycle comprises a coordinated series of events that carry cells from their quiescence/resting state (G0) to proliferation while maintaining their genetic constitution. It consists of four distinct phases: G1, S, G2, and M [66]. The S or the DNA synthesis phase and the M or the mitotic phase are separated from each other by the gap phases G1 and G2. Entry into the cell cycle (G1) from G0 occurs in response to a mitogenic stimulus usually through an upstream receptor tyrosine kinase. Regulation of transition through the various cell cycle phases occurs through coordinated expression of proteins called cyclin-dependent kinases (CDKs) and their associated partner proteins called cyclins. The expression of specific cyclin/CDK pairs regulates either the transition or non-transition of cells in a particular cell cycle phase, as shown in Fig. 1. In addition to regulation by the CDKs/cyclins, cell cycle progression is also monitored through checkpoint proteins that are primarily activated in response to DNA damage as well as signaling through tumor suppressor and antiapoptotic proteins. These so-called checkpoints exist at G1–S, intra-S, and G2–M transition phases [67]. The cumulative effect of these regulatory checkpoints and their interactions decide cell fate: to undergo proliferation or apoptosis. Cells can also exit the cell cycle and enter a reversible or permanent cell cycle arrest (the G1 or G2 phase) or senescence.

3.3.1 The Cyclin–CDK–Rb Axis

Nine CDKs (CDK1–9) and cyclins (A–T) regulate different processes in the cell cycle through formation of specific cyclin/CDK complexes. Progression of cell cycle phases is regulated by sequential synthesis and degradation of CDK partner cyclins. Cell cycle progression is negatively regulated by CDKi that inhibit cyclin/CDK complex activity. The CDKi belongs to either the INK4 (p16Ink4a, p15Ink4b, p18Ink4c, and p19Ink4) or CIP/KIP (p21Waf1, p27Kip1, and p57Kip2) family of proteins that target specific cyclin/CDK complexes. The INK4 CDKi binds to CDK4/6 and blocks their association with D-type cyclins, inactivating the kinase activity of CDK4 and CDK6. Similarly, the CIP/KIP CDKi binds and inhibits the kinase activity of CDK2 and CDK1, thus maintaining cellular homeostasis. The CDKis are, in turn, positively regulated by various tumor suppressor proteins—p53, SMAD4, etc. [66, 67].

Initiation of cell cycle progression from G0 to G1 starts with activation of the cyclin D/CDK4/6 complex, which acts by two major mechanisms: first, by sequestering the CDKis p21CIP1 and p27KIP1 and, second, by phosphorylating various cellular targets, including the retinoblastoma (Rb) tumor suppressor protein [14]. Closely related Rb proteins that include RBL1 or p107 and RBL2 or p130 can also be phosphorylated by this complex. These phosphorylation events lead to activation of the cyclin–CDK–Rb pathway that ends with activation of the transcription factor E2F. In its active state (tumor suppressive function), Rb is hypophosphorylated and inhibits the transcription factor E2F by binding to it. Phosphorylation of Rb by cyclin D/CDK4/6 releases E2F that, in turn, transcribes a group of genes involved in cell cycle progression from the G1 into the S phase. Included amongst these genes are cyclin E1 (CCNE1) and cyclin E2 (CCNE2) that drive the progression of cells from the G1 to the S phase. Other genes transcribed by E2F regulate DNA replication, chromatin structure, chromosomal segregation, spindle assembly checkpoint (SAC), centromere organization proteins, etc. during progression of the S phase. Cyclin E1/E2 bind to and activate CDK2. Cyclin E–CDK2 complexes further phosphorylate Rb. This hyperphosphorylation event serves as a positive feedback loop, further driving the cell cycle [67]. Thus, the cyclin D1–CDK4/6–Rb axis drives progression through the G1 stage and the cyclin E–CDK2–Rb axis drives the S-phase transition and progression. Negative regulators of the cyclin E–CDK2 complexes include p27KIP1 and p21CIP1 that, in turn, are regulated by growth-inhibitory signals and the p53-dependent G1 DNA damage checkpoint CHK2. Progression from the G2 phase to mitosis (the M phase) is controlled by cyclin A2/CDK1 and cyclin B/CDK1 complexes. During the G2 phase, CDK1 binds to and becomes activated by cyclin A2 and cyclin B. Upon entry into mitosis, cyclin A2 is degraded and CDK1 activity is maintained in complexes with B-type cyclins. The CDK1 kinase is essential for mitotic entry and several mitotic events. B-type cyclins are degraded by the anaphase-promoting complex/cyclosome (APC/C) in late mitosis, leading to the termination of the mitotic phase [27, 68]. Inactivation of CDK1 through degradation of cyclin B enables chromosomal separation and cytokinesis, thus completing the cell cycle. At the G2 phase, CDK1 activity is regulated through kinases MYT1 and WEE1, which, in turn, are negatively regulated by CDC25 phosphatases [69, 70]. The non-cycle CDK/cyclin complexes include CDK5 (cyclin D/E/G), CDK7 (cyclin H), and CDK9 (cyclin T, K). These kinases function to regulate senescence, CDK-activating kinase transcription, and transcription of pro-proliferative proteins, respectively [67, 71].

3.3.2 DNA Damage Response Checkpoints

DNA damage response during any phase of the cell cycle is initiated with the detection of DNA damage by sensor proteins. Cells have specific DNA damage response checkpoints that halt cell cycle progression till DNA repair is accomplished. A majority of these DNA damage checkpoints influence the activity of specific CDK complexes, as shown in Fig. 2 [71]. Depending on the type of DNA damage, the sensor proteins that include the MRE11–RAD50–NBS1(MRN) complex, RAD17, etc. activate the transducer proteins (e.g., ATM, ATR, etc.) that, in turn, transduce the signal to effector proteins—checkpoint kinase 1 (CHK1) and CHK2. Activated CHKs, in turn, switch "on" a cascade of events, leading to cell cycle arrest, apoptosis, DNA repair, and/or activation of DNA damage-induced transcription machinery. In the absence of an efficient checkpoint system, unrepaired damages go undetected, leading to mutations and genomic instability that supports oncogenesis.

Each step in DDR is tightly regulated. Kinases belonging to the phosphatidylinositol-3-kinase (PI3K) superfamily ataxia-telangiectasia mutated kinase (ATM); ATM- and Rad3-related kinase (ATR); and DNA-dependent protein kinase (DNA-PK) catalytic subunit are the primary transducers of DDR. On activation by phosphorylation, both ATM and ATR act as regulators of the DDR by affecting DNA replication, DNA repair, DNA recombination, transcription, and protein metabolism and cell cycle progression. DNA-PK interacts with the DNA-binding Ku 70/80 heterodimer, pushing the cells to undergo DNA repair via the non-homologous end joining (NHEJ) repair pathway with consequent introduction of erroneous DNA that may support oncogenesis. ATM and ATR protein kinases phosphorylate and activate the effector kinases—checkpoint kinase 1 (CHK1) and CHK2—which, in turn, phosphorylate their downstream target proteins that include p53, MYT1, CDC25, etc. [71–73].

DNA damage effector checkpoints CHK2 and CHK1 act at the G1–S and G2–M transition phases, respectively [71]. At the G1–S transition, downstream activation of the tumor suppressor p53 via CHK2 induces expression of the CDKi p21CIP1 that, in turn, inhibits cyclin E–CDK2 or cyclin A/B–CDK1 complexes, leading to G1 or G2 arrest. Progression from the G2 to the M phase is regulated by activation of cyclin A/B–CDK1 complex that requires phosphorylation at threonine. Activation of the cyclin B–CDK1 kinase requires dephosphorylation of CDK1 at Thr14 and Tyr15, and phosphorylation at Thr161 is mediated by CDC25 phosphatase and cyclin H/CDK7, respectively. At the G2–M checkpoint, CHK1 kinase suppresses CDC25 phosphatase activity, resulting in the simultaneous activation of Myt1 and WEE1, both of which mediate temporary S-phase arrest through the G2 checkpoint by phosphorylation of CDC25A, CDC25B, CDC25C, and CDK1 inactivation, thus allowing cells to repair the DNA damage (see Fig. 2). CHK1 is thus negatively regulated by the CDC25 phosphatase that inacti-

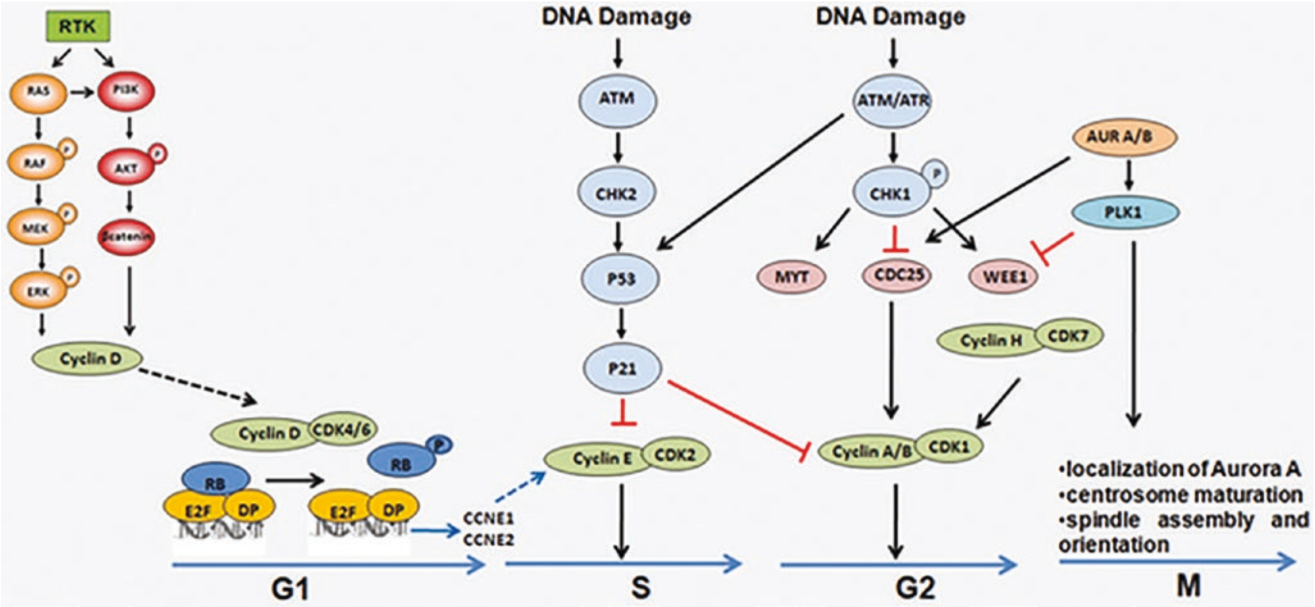

Fig. 2 Regulation of cell cycle progression and the role of DDR [67, 71]

vates Myt and WEE1 by dephosphorylation, thus releasing the negative proliferation controls on cyclin A/B–CDK1 complexes and allowing cell cycle progression. Inhibition of CHK1, WEE1, or MYT1 in cancer cells prevents cell cycle arrest during the S or G2 phase and enables cell proliferation despite accumulation of DNA damage that can lead to mitotic catastrophe and cell death during the M phase [74]. Positive regulation of CDK1 is mediated via polo-like kinase 1 (PLK1) and Aurora kinases. PLK1 activates CDK1 by suppression of CHK1 activity through phosphorylation-dependent degradation of WEE1 and activation of CDC25. PLK1, in turn, is regulated by Aurora A kinase, thereby promoting CDK1 activation and mitotic entry overcoming the G2–M checkpoint. Aurora kinases are serine/threonine kinases that regulate mitosis and cytokinesis. Aurora A localizes to the centrosomes, starting in the S phase, and is essential for centrosome maturation, spindle assembly, and spindle orientation in the M phase. Additionally, it stabilizes the transcription factor NMYC (encoded by MYCN) by preventing its proteasomal degradation and thereby promotes G1–S progression. Aurora B localizes at chromosomes and at the mitotic spindle during the M phase, where it constitutes a part of the chromosomal passenger complex (CPC). Aurora B controls chromosomal condensation and orientation as well as proper execution of cytokinesis. Bypass of the G2–M DNA damage checkpoint through Aurora kinase-mediated PLK activation leads to cellular mitotic catastrophe in the resultant phenotype [74–76].

In most cancer cells, the G1–S checkpoint CHK2 is dysregulated, leading to bypass of this check signal and continuation of the cells into the S phase before repair of the damaged DNA. This gives cancer cells a means to accumulate oncogenic mutations that favor proliferation and evasion of apoptosis. In the absence of the G1–S checkpoint, cancer cells are dependent on the G2–M checkpoint to prevent excessive DNA damage that may lead to apoptosis via mitotic catastrophe. The G2–M checkpoint thus works in favor of tumor cell survival, and, hence, inhibition of the G2–M checkpoint will prove detrimental to tumor cells [77, 78]. Such a drug target strategy will also provide for a higher therapeutic index as it will selectively target tumor cells with sparing of normal cells that have functional G1 and G2–M checkpoints. In addition to the G2–M checkpoint, G2–M regulatory kinases—Aurora kinases, PLK, WEE1 that participate in DDR—serve as attractive targets in cancer [79].

Given their role in the regulation of proliferation, several cell cycle checkpoint proteins have been used to obtain therapeutic drugs, examples of which are provided in Table 5 [71, 77–79].

Table 5 Cell cycle regulators in clinical development

Drugs	Target	Clinical trial status
Dinaciclib	CDK2, CDK5, CDK1, CDK9, CDK7, CDK6	Phase III: chronic lymphocytic leukemia (CLL) Phase II: Melanoma, CLL, lung, breast, and multiple myeloma
R-roscovitine (seliciclib)	CDK2, CDK7, CDK1, ERK2	Phase I: Advanced solid tumors
Palbociclib (PD0332991)	CDK4, CDK6	Approved for HER2-negative breast cancer in combination with aromatase inhibitors
Abemaciclib	CDK4, CDK6	Approved for hormone receptor-positive, HER2-negative advanced metastatic breast cancer both in combination with fulvestrant and as a monotherapy
Ribociclib (LEE011)	CDK4, CDK6	Approved as a combination therapy with aromatase inhibitors for indications similar to those of palbociclib
MK-8776 (Scheme 900776)	CHK1, CDK2, PIM1	Phase II: AML Phase I: Non-Hodgkin's lymphoma
LY2606368	CHK1, CHK2, RSK1, MELK, SIK, BRSK2, and ARK5 (64 nM)	Phase II: Breast, ovarian, prostate, and lung Phase I: Head and neck, AML, and Myelodysplastic syndrome (MDS)
AZD1775 (MK-1775)	WEE1, YES1	Phase II: Lung, ovarian, pancreatic, stomach, AML, MDS, and head and neck Phase I: Head and neck, glioma, pancreatic, cervical, CML, AML, and bladder
Rigosertib (ON 01910. Na)	PLK1, PDGFR, Bcr-Abl, FLT1, SRC, FYN, PLK2, and CDK1	Phase III: MDS and pancreatic Phase II: MDS, AML, ALL, CML, ovarian, and squamous cell
Volasertib (BI 6727)	PLK1, PLK2, and PLK3	Phase III: AML Phase II: AML, MDS, lung, ovarian, and urothelial
Alisertib (MLN8237)	Aurora A, EPHA2	Phase III: Peripheral T-cell lymphoma Phase II: Lymphoma, lung, breast, ovarian, prostate, AML, gastroesophageal, melanoma, multiple myeloma, uterine, head and neck, mesothelioma, neuroblastoma, MDS, rhabdoid, and urothelial
AMG 900	Aurora C, Aurora B, Aurora A, and p38α	Phase I: AML and advanced solid tumors

3.4 Avoiding Immune Destruction

Avoiding immune destruction is an emerging hallmark in cancer that is widely acknowledged in the process of tumorigenesis. Both tumor cell features and the tumor microenvironment (TME) can modulate immune vigilance in cancers. Tumor cell features that aid in the evasion of immune surveillance include lack of costimulatory surface molecules such as B7 for antigen presentation, resulting in T-cell anergy, reduced expression of major histocompatibility complex (MHC) class I or class II receptors, expression of FasL (Fas ligand) that aid in apoptosis of T cells, expression of mucins that mask the tumor-specific antigens and release of cytokines (TGF-β, VEGF, etc.). A progressive alteration of an immune-suppressive TME is highly regulated through inflammatory cytokines and immunosuppression by selective infiltration of regulatory T cells (Tregs). Immune surveillance can monitor and subsequently eliminate tumor cells through recognition of tumor-specific antigens or antigens that are differentially expressed between cancer and normal cells. This immune response is elicited in the form of a strong inflammatory response that results in accumulation of specific cytokines and lymphocytes (tumor-infiltrating lymphocytes) and natural killer (NK) cells at the tumor site. Inflammatory modulation of the TME may either suppress or support tumor growth depending upon the TME and tumor–TME interactions. Chronic inflammation is reported to support tumor proliferation and to play a significant role in tumor immunosuppression and T-cell proliferation. It contributes to tumor survival and proliferation, provides extracellular matrix-modifying factors that aid in angiogenesis as well as in invasion and metastasis [80]. The most notable cytokines that induce immunosuppression include VEGF and TGF-β. VEGF levels and overexpression of VEGFR, in addition to their role in angiogenesis, have emerged as notable players in the regulation of TME's immune components. Increased expression of VEGF reduces the trafficking, proliferation, and effector functions of T lymphocytes, increases differentiation, proliferation, and density of Tregs that, in turn, negatively regulate cytotoxic T (Tc) cells and thus eliminates tumor cells, increases the number of immunosuppressive tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), and inhibits maturation of dendritic cells that, in turn, function in the priming of T-helper (Th) cells. VEGF can also increase the expression of the checkpoint proteins (PD-1, CTLA-4, Tim-3, Lag-3) on antitumor T lymphocytes, priming these cells to targeting by the Tregs. Trafficking of immune cells and tumor–stromal cell interactions by VEGF is regulated through expression of adhesion molecules, including the integrin ligands intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion protein 1 (VCAM1), on endothelial cells (ECs) and immune cells. Hence VEGF/VEGFR inhibitors may be effective in immune targeting of tumors. Several of these agents are already approved as anticancer agents and include bevacizumab, sunitinib, etc. [81–84]. These agents in combination with immunotherapies are under various stages of clinical development (clinicaltrials.gov; NCT02348008, NCT03475004, etc.). Another cytokine TGF-β secreted by the tumor cells can bring about similar immune suppression by increasing the recruitment of Tregs and suppressing the tumor suppressive effector cells (Tc and Th) [80]. Other chemokines secreted by tumor cells, such as C–C motif chemokine ligand (CCL)2, CCL28, CXCL8, CXCL12, ANG2, PlGF, and adenosine promote the recruitment of immunosuppressive cells as well as angiogenesis, thus changing the cellular balance of the TME [85].

Cancer-related inflammation contributes not only to the evasion of the immune response by the tumor cells but also provides pro-proliferative, metastatic, and angiogenesis capabilities to the tumor through TME modulation. Hence, new therapeutic options tailored to interfere with inflammation in the TME are being tested. These strategies include reeducating the TME through metabolic targeting, inhibiting inflammatory mediators or their downstream signaling molecules, blocking the recruitment of myeloid cells, and modulating immunosuppressive functions. Cytokine therapy with interleukin-2 (IL-2) in renal cell carcinoma and with interferon (IFN)-γ and IFN-β in hairy cell leukemia and high-risk melanoma, respectively, has demonstrated clinical benefits [85]. Several cancer vaccines that can generate new antigen-specific T-cell responses and amplify existing responses have been developed and these include Sipuleucel-T, Talimogene laherparepvec (T-VEC), etc. [86]. The concept of differential expression of tumor and normal cell surface antigens forms the basis for designing monoclonal antibodies as an effective immunotherapy, for example, targeting of tumor growth factor receptor HER2 with Herceptin. Immunomodulation through "adoptive T-cell therapies" that harness the tumor-killing properties of T cells are being tested to restore antitumor immune cell population. The therapy involves isolation, expansion, and genetic engineering of autologous T cells to express tumor-specific recognition receptors that include both conventional T-cell receptors (TCRs) and synthetic constructs called chimeric antigen receptors (CARs) [87]. Destruction of an active immunosuppressive T-cell population is mediated through activation of negative regulatory pathways, also known as immune checkpoints (CTLA-4, PD1, PDL-1) by tumor cells. Targeting immune checkpoints that negatively regulate cytotoxic T cells is thus an attractive strategy to maintain a positive immune pressure on tumor cells. The development of anti-CTLA4, anti-PD-1, and anti-PDL1 monoclonal antibodies that elicit antitumor clinical responses in a variety of solid cancers has solicited the inclusion of these immunotherapies in cancer treatment, and several of these antibodies are approved for cancer treatment (pembrolizumab, ipilimumab, nivolumab, etc.) [88].

Metabolic reprogramming of tumor cells can create a hostile TME for antitumor immune cells through glucose and amino acid depletion, hypoxia, high acidity through extracellular lactate release, etc., thereby reducing their activation and proliferation. Various metabolic nodes can be targeted for restoration of effective immune response to tumor cells that include regulation of aerobic metabolism [glucose transporter (GLUT), PI3K inhibitors], inhibition of lactate production [lactate dehydrogenase (LDH) inhibitors], etc. [89]. Additionally, novel metabolic targets such as indoleamine 2,3-dioxygenase-1 (IDO1) that degrade tryptophan to kynurenine, an immunosuppressing metabolite that acts as immune breaks, are being used in immunotherapy [90].

3.5 Cancer Invasion and Metastasis

Tumor spread from the primary site of origin to secondary sites of colonization, commonly referred to as invasion and metastasis, is a widely manifested clinical problem and one of the major hallmarks of cancer. This process is executed as a cascade of events, with each event being characterized by specific molecular changes in the tumor cells and TME. The major processes in malignancy are invasion, intravasation, extravasation, and colonization of a secondary metastatic niche. Invasion is characterized by the loss of cell–cell adhesion capacity (epithelial-to-mesenchymal transformation or EMT), maintained by epithelial cellular junctions (tight junctions, adherens junctions, gap junctions, desmosomes, and integrins), and alterations of the tumor cell–basement matrix. The major features of an EMT include loss of epithelial markers, such as E-cadherin, α-catenin, claudins, occludin, and zonula occludens-1 (ZO-1), an increased expression of mesenchymal markers, such as N-cadherin, vimentin, and fibronectin, and a reorganization of the cytoskeleton [e.g., loss of epithelial protein lost in neoplasm (EPLIN)] [91, 92]. EMT-inducing signals are initiated by growth factors—hepatocyte growth factor (HGF), epidermal growth factor (EGF), and transforming growth factor-β (TGF-β)—that, in turn, induce downstream activation of EMT transcription factors that include Snail, Slug, Twist, and zinc-finger E-box binding homeobox 1 (ZEB1) as well as activation of matrix metalloproteinases (MMPs) that degrade a variety of basement matrices [92, 93]. EMT-inducing transcription factors and inflammatory cytokines such as nuclear factor kappa B (NF-κB), IL-4, CCL5, etc. guide most of the steps in the invasion–metastasis cascade [94]. Finally, the seeding of circulating tumor cells into a secondary site is facilitated by a supportive stroma that arises in a primary tumor and a permissive TME composed of stromal support cells at the metastatic site such as the stromal-derived factor 1 (SDF1)–CXC motif chemokine receptor 4 (CXCR4) chemokine axis [94]. Metastasis is thus a highly complex process regulated through oncogenes and tumor suppressors, genomic instability, inflammatory cytokines, proangiogenic factors, transcription, metabolic alterations (hypoxia, pH, etc.), and tumor stromal interactions that promote the establishment of tumor cells at secondary sites [95]. Targeting metastasis is thus a challenging task, and the therapeutic aim should be prevention of an initial/additional metastasis in high-risk patients and shrinkage of established lesions. This would involve a multimodal treatment approach comprising a combination of distinct drug class molecules, with regular monitoring for minimal residual disease. Given the challenges in designing an appropriate treatment strategy, metastasis seems an extremely tough condition to deal with. Targeting metastasis with denosumab, a monoclonal antibody that blocks the receptor activator of the NF-κB ligand (RANKL), has shown clinical benefit in solid tumor patients with bone metastases. Denosumab is FDA-approved for prevention of skeletal-related events (SREs) in solid tumors and as an adjuvant therapy in prostate cancer [96, 97]. Other prospective drug development programs targeting metastasis include Bevacizumab (anti-VEGF), Cilengitide (αvβ3 and αvβ5 integrin peptide inhibitor) and SRC/Bcr-Abl dual-kinase inhibitors dasatinib and saracatinib [97].

4 Conclusions

Translational oncology research in the areas of oncogene addiction, tumor suppression, cell cycle regulation, immune tumor cell interaction, and metabolic reprogramming of the TME has led to the emergence of an arsenal of drugs for treating cancers in the last few decades. These key areas continue to hold a huge potential for addressing unmet medical needs and therapeutic progress in the practice of oncology.

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Surgical Oncology

Gouri Pantvaidya and Abhay Kattepur

Abbreviations

FAP	Familial adenomatous polyposis
FNAC	Fine needle aspiration cytology
GA	General anesthesia
MEN	Multiple endocrine neoplasia

1 Introduction

Surgical oncology (also called oncological surgery) is a surgical specialty dealing with the surgical management of cancerous and tumorous conditions. It is one of the oldest, curative modalities of cancer therapy. Oncological surgery is now recognized as a specialized and advanced field of surgery that requires dedicated training and practice. Significant changes in oncological surgery have occurred in recent decades. The two broad changes in oncological surgery have been the incorporation of surgery as part of the treatment algorithm with other modalities of treatment (rather than the only form of treatment) for solid tumors and the need to super-specialize in various subspecialties within this vast field like head and neck oncology, breast oncology, gynecological oncology, thoracic oncology, gastrointestinal oncosurgery, musculoskeletal oncology, etc. Oncological surgery encompasses guiding principles, improved perioperative care, minimally invasive techniques, and a special emphasis on expedited recovery principles. There has also been a shift toward the increased use of conservative and minimally invasive surgery with an aim to decrease morbidity without compromising disease outcomes.

Oncological surgery is a vast topic, and its complete description is beyond the purview of a single chapter. This chapter aims to outline the fundamentals and guiding principles of oncological surgery in the management of solid tumors.

2 Historical Perspective

- Earliest description of surgical extirpation of tumors: Edwin Smith papyrus from the Egyptian Middle Kingdom (circa 1600 BC)
- McDowell: First elective surgery for visceral tumors in 1809
- John Collins Warren: Submandibular gland excision in 1846 under general anesthesia
- Other important milestones have been depicted in Table 1.

Table 1 Major milestones in the field of oncological surgery

Year	Name	Contribution
1867	Joseph Lister	Introduction of antisepsis
1860–1890	Albert Theodore Billroth	First gastrectomy, laryngectomy, esophagectomy
1878	Richard von Volkmann	Excision of cancerous rectum
1880s	Theodore Kocher	Development of thyroid surgery
1890	William Halsted	Radical mastectomy
1896	G. T. Beatson	Oophorectomy for breast cancer
1904	Hugh H. Young	Radical prostatectomy
1906	Ernest Wertheim	Radical hysterectomy
1908	W. Ernest Miles	Abdominoperineal resection for rectal cancer
1912	E. Martin	Cordotomy for the treatment of pain
1910–1930	Harvey Cushing	Development of surgery for brain tumors
1913	Franz Torek	Successful resection of cancer of the thoracic esophagus
1927	G. Divis	Successful resection of pulmonary metastases
1933	Evarts Graham	Pneumonectomy
1935	A. O. Whipple	Pancreaticoduodenectomy (Whipple's surgery)
1945	Charles B. Huggins	Adrenalectomy for prostate cancer
1958	Bernard fisher	Organization of the National Surgical Adjuvant Breast and Bowel Project (NSABP) to conduct prospective randomized trials

From Ref. [1]

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3 Operative Risk Assessment

Operative risk is a combination of operative mortality and major morbidity. “Operative mortality” is usually defined as mortality occurring within 30 days of any surgical procedure. Morbidity and complications of surgery are now well-documented for most oncological procedures. Numerous classification systems are available for classifying the grades of complications, and most solid tumor surgeries have specific validated instruments for each subsite. Examples include the ISGPS (International Study Group of Pancreatic Surgery) definition and grading of postoperative pancreatic fistula [2] or the ECCG (Esophagectomy Complications Consensus Group) definition and grading of anastomotic leak [3] (Table 2). However, the most commonly used system to grade complications is the Clavien–Dindo classification of surgical morbidity [4–6] (Table 3). This classification has been validated across many oncological solid tumor surgeries [7–9].

An understanding of the expected complication rates and associated morbidity and mortality from surgeries being performed for cancers is vital in preoperative counseling and decision-making to choose the correct treatment options for patients. Unlike non-oncological surgery, the balance between disease outcomes and morbidity of surgery has to be titrated prior to embarking on extensive procedures.

3.1 Preoperative Fitness Assessment and Operative Risk Prediction

Operative risk assessment involves many components of care such as patient-related factors, performance status, surgical factors, anesthetic techniques, etc.

The American Society of Anesthesiologists (ASA) has developed a classification/grading of the physical fitness of patients undergoing surgery [10, 11]. This is the commonest and most robust form of assessment to evaluate physical fitness for surgery. Patients are grouped as ASA 1–5 (Table 4).

There are numerous operative risk stratification systems, which have been validated for solid tumor surgery. The POSSUM (Physiology and Operative Severity Score for the enUmeration of Mortality and morbidity) risk stratification

Table 3 Clavien–Dindo grading of postoperative complications

Grade	Description
Grade I	Any deviation from the normal postoperative course with no need for pharmacological, radiological, surgical, or endoscopic interventions Drugs that can be used: antiemetics, antipyretics, analgesics, diuretics, and electrolytes Also includes wounds that have been opened bedside for drainage
Grade II	Use of drugs (other than those listed under grade I), parenteral nutrition, and blood and blood products
Grade IIIa	Requires surgical/endoscopic/radiological intervention not under general anesthesia (GA)
Grade IIIb	Requires surgical/endoscopic/radiological intervention under GA
Grade IVa	Life-threatening complication needing intensive care unit (ICU) care with single organ dysfunction (includes dialysis)
Grade IVb	Life-threatening complication needing ICU care with multiple organ dysfunction
Grade V	Death of the patient
Suffix “d”	Added to indicate “disability” when the patient suffers from any of the above complications at the time of discharge

GA general anesthesia

Table 4 ASA grading of risk

Class	Description
I	Patient is completely healthy and fit
II	Patient has mild systemic disease
III	Patient has severe systemic disease that is not incapacitating
IV	Patient has incapacitating disease that is a constant threat to life
V	A moribund patient who is not expected to live 24 h with or without surgery
E	Emergency surgery. E is placed after the Roman numeral

From Ref. [11]

Table 2 Definition and grading of complications

Group	Definition	Grades	
ISGPS	Drain output of any measurable volume with an amylase level more than three times the upper limit of institutional normal serum amylase associated with a clinically relevant condition directly related to the postoperative pancreatic fistula	A B C	Biochemical leak, no clinical outcomes Change in the postoperative management: drains either left in place >3 weeks or repositioned through endoscopic or percutaneous procedures Requiring re-surgery or leading to single or multi-organ failure and/or mortality
ECCG	Full thickness defect involving the esophagus, anastomosis, staple line, or conduit irrespective of the presentation or method of identification	I II III	Local defect requiring no change in therapy, treated medically, or treated with dietary modification Localized defect requiring interventional but not surgical therapy Localized defect requiring surgical therapy

system was described for patients undergoing surgical procedures. This score has been validated in many solid tumor surgeries and has shown a good predictive value for postoperative morbidity and mortality [12–14].

Most of the scoring systems for morbidity or mortality use a combination of the following criteria.

- *Age of the patient*: Increasing age is directly proportional to the risk of postoperative complications. The risk of postoperative mortality is 30–35 times higher in patients aged more than 70 years of age compared to their younger counterparts.
- *Comorbidities*: As the number of comorbidities increase (also related to the increasing age of the patient), the risk of morbidity and mortality increases. For example, diabetic patients run the risk of infections, dyselectrolytemias, and gastroparesis.
- *Poor nutritional status*: Albumin levels correlate directly with postoperative outcomes, especially for major gastrointestinal surgeries. Low albumin levels result in poor wound healing and increase the risk of anastomotic leaks.
- *Cancer cachexia*: This is an extreme form of malnutrition characterized by weight loss and sarcopenia seen in advanced cancers and contributes to poor outcomes after palliative surgeries in such patients [15].
- *Addictions*: Smoking increases the risk of postoperative mortality by 1.5–4-fold. It impairs wound healing and affects ciliary epithelium functioning, resulting in infections and respiratory infections.
- *Multiple prior surgeries*: These increase the risk of morbidity postoperatively.
- *Prior chemotherapy/radiotherapy*: Many patients with cancer undergoing surgery would be exposed to chemotherapy or radiotherapy prior to surgery. Chemotherapy increases the risk of postoperative infections (as total leukocyte counts fall), whereas radiotherapy increases the risk of infections and wound complications.
- *Increased body mass index (BMI)*: Obese patients with a high body mass index (BMI) are susceptible to pulmonary complications, thromboembolism, and delayed wound healing postoperatively with a 1–1.7 times higher risk of mortality [16].
- *Coagulopathies*: These include thrombocytopenia/hypercoagulable states resulting from cancer per se or part of the treatment increases the risk of postoperative morbidity and mortality by two- to threefold.

4 Diagnostic Biopsy in Solid Cancers

A diagnostic biopsy is used in a number of solid cancers. It is important to note that in most solid tumors, a diagnosis of cancer can be readily obtained by less invasive procedures like fine needle aspiration cytology (FNAC), which can be either clinician-performed or image-guided. Open biopsies are rarely recommended for diagnosis of solid tumors.

4.1 Types of Biopsies Performed

- *Open excision biopsy*: This is a type of biopsy, where the lesion or the node is excised in toto for obtaining a diagnosis (e.g., for better characterization of suspected metastatic lymph nodes that are inconclusive on FNAC), or excision biopsy of oral leukoplakias for obtaining histopathological diagnosis.
- *Tru-cut or core biopsy*: This is a biopsy, where a small core of tissue is removed from larger masses, using special needles (like the J needle or Jamshidi needle for bone biopsies) to help characterize the tumors better (e.g., core biopsy of breast cancers to perform immunohistochemistry for biomarkers [estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER2)-neu) for therapy]. These biopsies may be performed with image guidance in cases of inaccessible tumors.
- *Endoscopic biopsy*: These biopsies are performed for tumors within luminal organs (e.g., colonoscopic biopsy for colonic cancers).

4.2 Principles of Performing Biopsies in Solid Tumors

- Avoid an open biopsy whenever feasible.
- Use noninvasive techniques of obtaining diagnosis like an FNAC, prior to deciding to perform a biopsy.
- If the FNAC is inconclusive or better characterization of tumors is required, then perform a biopsy.
- Discrete lymph nodes in accessible locations are best removed as a complete node.
- Perform a core biopsy for larger masses.
- Use image guidance [ultrasonogram (USG)/computed tomography (CT) scanning] when biopsies are to be performed from inaccessible locations or if masses are close to critical anatomical structures like major blood vessels, trachea, etc.
- Plan incisions of biopsies in a way that these incisions can be excised within the scar of the proposed surgery.

5 The Role of Surgery

5.1 Preventive/Prophylactic Surgery

Preventive or prophylactic surgery is defined as the preemptive operative removal of an organ prior to malignant transformation or when the cancer is still in situ. It generally involves removal of the organ at risk so that future cancer can

Table 5 Prophylactic cancer surgeries

Condition	Cancer	Prophylactic surgery
Cryptorchidism	Testicular	Orchiopexy
Adenomatous polyposis coli	Colon	Total colectomy
Familial colon cancer	Colon	Colectomy
Ulcerative colitis	Colon	Colectomy
MEN syndrome 2	Thyroid (medullary)	Total thyroidectomy
Familial breast cancer	Breast	Mastectomy
Familial ovarian cancer	Ovary	Salpingo-oophorectomy
Hereditary diffuse gastric cancer	Diffuse gastric cancer	Total gastrectomy
Lynch syndrome	Endometrium Colon	Hysterectomy and colectomy

Modified from [1]

be prevented. Most prophylactic surgeries for malignancy are conducted because of the presence of a genetic mutation that has a high penetrance and is a known cause of the particular malignancy. Prophylactic surgeries and conditions are listed in Table 5.

5.2 Criteria for Prophylactic Surgery

- The genetic mutation involved in the disease process must have high penetrance.
- A highly reliable test to identify patients with these mutations should be present.
- The organ being removed must be associated with low morbidity.
- There should be a suitable replacement of the function of the organ being removed.
- A reliable method to determine whether that patient has been cured over time should be available.

5.3 Examples of Prophylactic Surgery

- MEN (multiple endocrine neoplasia) syndrome [17, 18], which includes MEN-1, MEN-2A, and MEN-2B, characterized by two or more endocrine tumors with an autosomal dominant pattern of inheritance. Patients with MEN-2 mutations have an increased risk of medullary thyroid cancers warranting prophylactic total thyroidectomy in these patients at an early age.
- Mutations of the breast cancer susceptibility genes (BRCA 1 and BRCA 2) are associated with the hereditary breast and ovarian cancer syndrome (HBOC) characterized by an increased risk of breast and ovarian cancers in affected individuals [19, 20] which may warrant prophylactic mastectomy and/or salpingo-oophorectomy.
- FAP (familial adenomatous polyposis) syndrome is characterized by hundreds to thousands of polyps carpeting the entire colon and often the rectum. The gene responsible is the APC gene on chromosome 5q21. These patients have an increased risk of colon cancer, thus warranting total colectomy at an early age, and also an increased risk of periampullary cancers, desmoids, and central nervous system (CNS) tumors [21].

6 Curative Surgery

Surgical extirpation of the tumor and the affected nodal basins remains the most effective method to cure patients with organ-confined solid cancers. Oncological surgery involves the removal of the primary tumor with gross and microscopic, pathologically negative margins along with removal of the draining lymph nodes.

6.1 Principles of Resection of the Primary Cancer

Research on the outcomes and factors predicting recurrence and survival in oncological surgery has made it possible to have guidelines for the extent of resection of primary tumors, for every subsite. The definition for adequate margins, need for prophylactic nodal dissections, extent of nodal dissection, and reconstructive procedures vary significantly across every tumor subtype. A knowledge and understanding of all of the above factors is required prior to embarking on any oncological surgery. Describing principles of resection for every subsite of cancer is beyond the scope of this chapter. Highlighted below are certain important basic surgical principles of oncological surgery.

- The primary tumor is to be excised in entirety, including the adjacent normal tissues as margins, to account for microscopic spread of the disease. All efforts to achieve pathologically adequate, cancer-free margins are a prerogative of any oncological surgery.
- The margins that are considered adequate have been defined for most solid tumors, and the surgeon should have a priori knowledge of what constitutes a negative margin before embarking on surgery for a particular cancer.
- Spillage, rupture, contamination, and excessive handling of the primary cancer are best avoided.
- During resection, all attempts should be made to spare important anatomical structures without compromising the margins of resection.
- Minimally invasive techniques of surgery should be used in indications where their use has shown to decrease post-

operative morbidity, without impacting disease outcomes. This is the most important in pelvic surgeries like prostatectomies, hysterectomies, and rectal cancer resections.

- The extent of surgical resection is categorized as:
  - R0: Complete removal of the tumor, with no gross or microscopic residual disease
  - R1: Complete removal of the tumor with the presence of microscopic residual disease
  - R2: Incomplete tumor removal with the presence of gross macroscopic residual disease

The importance of categorizing every oncological surgery as R0, R1, or R2 stems from the fact that in most solid cancers, completeness of resection is among the most important prognostic factor to predict both recurrence and survival. Patients undergoing R1 resections generally need adjuvant therapy to sterilize the margins in order to avoid local recurrences. Those undergoing R2 resections have poor oncological outcomes with survival rates similar to those who have not undergone resections, e.g., pancreatic cancer patients who undergo R2 resections show poor survival rates in comparison to those undergoing R0 resections [22–24]. In certain tumors like ovarian cancer, tumor debulking and leaving back minimal residual disease followed by adjuvant chemotherapy have been shown to have acceptable results [25]. However, in most other cancers, surgery should be deferred if the clinical examination and radiological imaging suggest a high probability of R2 resections.

6.2 Minimally Invasive Surgery in Oncology

Minimally invasive surgery is slowly and steadily making its foray into oncology. Any oncological procedure may be performed using the principles of minimally invasive surgery. Minimally invasive surgery can be performed by two methods, namely, laparoscopic or robotic, depending on the availability of expertise and equipment. Both methods combine the benefit of potential oncological safety with the advantages of lesser postoperative pain, early discharge from the hospital (reduced hospital stay), and smaller incisions. However, they come at the expense of increased operative cost and time, need for specialized training, and expertise to perform the procedure. Minimally invasive surgery should be performed in indications where there is a proven benefit of these procedures either in decreasing postoperative morbidity and hospital stay or improving quality of life. Cancers of the colorectum, esophagus, and stomach are increasingly being performed using minimally invasive approaches with equivalent oncological outcomes as traditional open surgeries [26].

6.3 Resection of Metastatic Disease

Common sites of metastases from solid tumors include the lungs, liver, and bone. In most cancers, the presence of distant metastases to these organs portends an extremely poor prognosis for patients. Resection of metastatic disease is generally performed for two indications

1. To improve oncological outcomes by resection of the metastases, e.g., resection of pulmonary metastases in soft tissue sarcomas has shown to improve survival. In a study by Belal et al. [27], the 5-year overall and disease-free survival of patients undergoing metastasectomy was 24% and 21%, respectively, indicating that such patients had improved survival outcomes. Similarly, resection of hepatic metastases in colorectal cancers has shown improvement in survival ranging from 35 to 60% [28–30].
2. To relieve symptoms caused by metastatic disease, e.g., resection of metastases causing impending fractures, in weight-bearing bones like the femur, tibia, etc. and decompression and fixation of spinal metastases causing neurological impairment. Life-threatening brain metastases from cancers like thyroid cancers can also be undertaken.

The general principles of resection of metastatic disease include [31]

- Resection has better results for oligometastases rather than for multiple metastases.
- A complete resection of the metastases should be deemed feasible prior to embarking on surgery.
- The primary cancer should be controlled or easily controllable at the time of metastasectomy.
- Disease-free interval (DFI) plays an important role in determining outcomes after a metastasectomy. The longer the DFI, the better are the outcomes of metastasectomy.
- There are better outcomes for metachronous rather than synchronous presentation.
- Patient- and tumor-related factors should be taken into consideration prior to deciding on a metastasectomy.
- Metastasectomy is best avoided in patients who have aggressive malignancies, multiple metastases, a poor DFI, and multiple comorbidities.

7 Reconstructive Surgery in Oncology

After oncological resections, restoring cosmesis and function remains a tremendous challenge. This is especially so for surgeries involving head and neck and breast cancers.

Functional rehabilitation after ablative surgery for the oral cavity and laryngopharynx is a big challenge. With improvements in microvascular surgery and prosthetic implants, reconstruction of complex defects is now feasible.

7.1 Principles of Reconstructive Surgery [32]

- Preoperative planning along with estimation of functional and cosmetic deficits is mandatory.
- As far as possible, “like tissues to be replaced with like,” e.g., reconstruction after mandibular resection should be done using a bone flap rather than just a muscle-based flap.
- Reconstruction of all components of excision should be attempted.

8 Palliative Surgery

- Used for pain relief or restoration of function
- Can improve quality of life in these patients with advanced cancers
- Certain examples include (1) palliative bypass in case of intestinal obstruction; (2) toilet mastectomy for removing fungating/bleeding breast cancers; and (3) removal of masses causing intractable pain.
- Usually associated with high morbidity and mortality in view of advanced cancer and poor performance status of patients.

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Radiation Oncology

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Abbreviations

ACR/ASTRO	American college of radiology/Americal society for therapeutic radiology & oncology
AVM	Arterio venous malformation
CTV	Clinical target volume
DSB	Double-strand break
EBRT	External beam radiation therapy
FSU	Functional subunit
GEC-ESTRO	Group European de Curitherapie European society for radiotherapy & oncology
GTV	Gross tumor volume
Gy	Gray
HDR	High dose rate
HVL	Half value layer
ICRU	International Commission on Radiation Units and Measurements
IMPT	Intensity-modulated proton therapy
IMRT	Intensity-modulated radiation therapy
ITV	Internal target volume
IV	Irradiated volume
LDR	Low dose rate
LET	Linear energy transfer
MDR	Medium dose rate
MLC	Multileaf collimator
OAR	Organ at risk
OER	Oxygen enhancement ratio
PRV	Planning organ at risk volume
PTV	Planning target volume
RB	Retinoblastoma
RBE	Relative biological effectiveness
RILD	Radiation induced liver disease
RTOG	Radiation therapy oncology group
SAD	Source-to-axis distance
SBRT	Stereotactic body radiotherapy
SRS	Stereotactic radiosurgery
SRT	Stereotactic radiotherapy
SSB	Single-strand break
SSD	Source-to-skin distance
TBI	Total body irradiation
TRAK	Total reference air kerma
TSET	Total skin electron therapy
TV	Treated volume
VMAT	Volumetric modulated arc therapy

1 The Discipline of Radiation Oncology

Radiation oncology is a specialized medical discipline that deals with expertise in the use of therapeutic ionizing radiation for the treatment of both benign and malignant conditions. The therapeutic effect of ionizing radiation stems from a close interaction of multiple factors like the physical properties of radiation, the biology of tumor and normal tissues, host immunogenic response, heat, oxygen, and other therapies like chemotherapy and surgery. The therapeutic goal of radiation oncology is to achieve maximum tumor cell kill while sparing the normal tissue of radiation damage, thereby widening the therapeutic ratio. Therapeutic radiation can be delivered either from a radiation source placed away from the target tissue, i.e., external beam radiotherapy/teletherapy, or from a radiation source placed into or extremely close to the target tissue, i.e., brachytherapy. Radiation in teletherapy could be derived from either the

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Table 1 Types of brachytherapy

Brachytherapy types	Sites
Interstitial	Breast, soft tissue sarcomas, vagina, prostate, anal canal, head and neck cancers
Intracavity	Uterine cervix, endometrial cancer
Intraluminal	Esophagus, bronchus, biliary tree
Endovascular	Peripheral vascular disease, stent restenosis
Surface mold	Head and neck cancers

spontaneous disintegration of a radioactive source like cobalt-60 (γ-rays) or artificially produced using linear accelerators (X-rays). Based on the way that the radiation source is placed in proximity to the target tissue, the technique of brachytherapy may be classified into five broad categories as enumerated in Table 1. Based on the rate at which the radiation dose is delivered, brachytherapy may be classified as a high dose rate (HDR) >12 Gy/h, a medium dose rate (MDR) 2–12 Gy/h, and a low dose rate (LDR) <2 Gy/h A typical prescription for radiotherapy treatment would include information on the total dose, the number of fractions of radiation, the dose per fraction, and the total duration of the treatment. The clinically relevant unit while reporting the dose of radiation is Gray (Gy). One Gray is defined as the absorption of one joule of energy per kilogram of matter. The SI (International System of Units) unit is J/kg^{-1}. Multiple factors like tumor biology, tolerance of the normal tissue, type of radiation used, and concurrent therapy along with radiation play a role when deciding the prescription dose for a particular tumor.

2 The Historical Aspects of Radiation Oncology

The history of therapeutic radiation dates back to 1895, when Wilhelm Conrad Roentgen discovered X-rays, which was immediately followed by the discovery of radioactivity by Marie Curie in 1898. Radium-226 was the first radioactive isotope to be used for medical treatment, but it fell out of favor due to potential hazards like leakage of the gaseous daughter radioactive product, radiation exposure to personnel (preloaded), dosimetric inconsistencies due to construction, etc. Cobalt-60 was used as an alternative to radium-226 in the 1950s [1]. Cobalt teletherapy units were used for many years before being gradually phased out in favor of the more versatile linear accelerators. In many institutions across India, cobalt-60 teletherapy machines still remain the workhorse due to their lower cost, simplicity of use, and low maintenance features compared to those of the more complex linear accelerators. The first linear accelerator with 8-MV photons was installed at the Hammersmith Hospital in London in 1952. The principal advantage of the initial linear accelerators was the higher energy of photons and the possibility to have beams of multiple energies. These accelerators did not have in-built beam-shaping devices. In 1968, Japanese scientists showed that it was possible to shape beams with the use of multileaf collimators (MLCs), thus producing a more conformal treatment field [2]. In 1978, automated computer-controlled linear accelerators were developed [3]; these are the cornerstone of radiotherapy today. The roots of image guidance for cobalt teletherapy units during radiation therapy to confirm the location of the target can be traced back to 1960 in London, and, later in 1985, it was incorporated into the modern linear accelerators [4]. In 1999, more refined image-guided feedback systems were developed [5]. The basic concept of intensity modulation has been used since 1959 [6], with the use of compensators and beam modifiers. It was in the 1980s and 1990s that computing technology developed significantly, leading to the development of modern intensity-modulated radiation therapy (IMRT) [7]. An exciting advancement in IMRT/image-guided radiotherapy (IGRT) was achieved in 1993, when TomoTherapy was developed by Mackie [8]. The proton was discovered in 1917 by Ernest Rutherford; in 1930, Ernest O. Lawrence developed the cyclotron to accelerate these protons for medical treatment. In 1954, the first patient with pituitary adenoma was treated with protons at the University of California, Berkeley, but the first hospital-based proton center was developed in 1990 in Loma Linda, California. Since its early inception, proton therapy has also evolved and now has much robust planning like intensity-modulated proton therapy (IMPT) [9]. In India, the history of radiation oncology started with the installation of the radium institutes in Patna, Agra, Madras, and Lahore. The first telecobalt machine was installed at the Adyar Cancer Institute in 1956 [10]. The first linear accelerator was installed in 1976 at the Adyar Cancer Institute [11]. According to the International Atomic Energy Agency-Directory of Radiotherapy Centres (IAEA-DIRAC), there are currently 352 radiotherapy centers in India with 264 linear accelerators [12].

3 The Biological Basis of Radiotherapy

3.1 Direct and Indirect Effects of Radiation

Radiotherapy affects tumor cells by the deposition of high physical energy of radiation in the irradiated medium [13]. When a photon enters the body, it can either pass through without any interaction or it can be completely absorbed or scattered based on the entry. The various types of interactions of photons with matter are presented in Table 2. The main target of damage in an irradiated cell is the DNA [14]. The physical interaction of radiation with the molecular structure of the cell lasts for only 10–30 seconds. The deposited energy can cause DNA damage in two ways—by direct and indirect mechanisms. In the direct mechanism, the incident radiation leads to the release of high-velocity electrons and secondary photons, thus causing direct damage to the DNA strands. In the indirect mechanism, the incident radia-

Table 2 Types of interactions of photons with matter [17]

Type of interaction	Energy range in water	Phenomenon
Photoelectric effect	Up to 25 keV	Interaction with the outer-shell electrons. Complete transfer of energy to the outer-shell electron, which leads to ejection of the electron from the orbit
Compton scattering	10–150 keV	Interaction with the inner-shell electrons. Absorption of a part of the energy, which leads to scattering of the photon and also expulsion of the electron
Pair production	>1.02 MeV	Interaction with the nucleus. The photon interacts with the nucleus to produce an electron and a positively charged positron

tion interacts with the water content of the cell, which constitutes up to 70–80%. This leads to the production of reactive oxygen species and free radicals, which contain an unpaired electron that makes them reactive. The majority of the effects due to radiation are caused by the indirect mechanism [15]. The number of free radicals produced by the ionizing radiation is a function of the dose [16].

3.2 Cellular Targets of Radiation

The main cellular target of radiation is the DNA. The damage caused by radiation on DNA can be of many types, such as double-strand breaks (DSBs), single-strand breaks (SSBs), protein DNA cross-linking, and multiple combinations. In DSBs, both the DNA strands are broken, whereas in SSBs, only one strand is broken. Based on the type of radiation, the numbers of DSBs and SSBs vary. When a cell is damaged by radiation, it reacts by arresting the progress in its cell cycle, activating apoptosis, or DNA repair. The major cell cycle checkpoints are the G1–S phase by the retinoblastoma (RB) gene, S phase, and G2 checkpoints. Based on the phase of the cell cycle, the process of repair starts. The two main methods of DSB repair are the homologous repair and the non-homologous end-joining repair. The choice for the type of repair depends on the position of the cell in the cell cycle. For homologous repair, there must be a template strand of DNA that is available only in the S and G2 phases. Thus, homologous repair predominates in the S phase. Homologous repair is the most accurate for repair, thus conferring radioresistance to the cells in the S phase. However, non-homologous end-joining repair is non-cell cycle-specific and is seen in all phases. Other forms of repair include base excision repair, mismatch repair, and nucleotide excision repair. If the cell is able to repair the DNA damage, then it progresses through the cell cycle. If not, then the process of apoptosis sets in, leading to apoptosis of the cell, which is known as interphase death. Apoptosis is mediated by the p53 gene. Some cells progress along the cell cycle but undergo death when trying to replicate by mitosis due to chromosomal aberrations. This is called mitotic death. Most of the cell deaths due to radiation occur as a result of mitotic catastrophe rather than the initial effect itself. A unique phenomenon seen in some cells is the bystander effect. This is cell death occurring in cells due to irradiation of the neighboring cells. This phenomenon can be explained by the secretion of certain toxic substances by the dying cells into the media or by the presence of gap junctions, which can facilitate the transfer of reactive oxygen species between cells. DNA damage can be classified based on the repair capacity. Lethal damage is that which cannot be repaired; potential lethal damage refers to that which can become lethal under suboptimal conditions but can be repaired under suitable conditions. Sublethal damage is that which can be usually repaired under normal conditions, but multiple sublethal damages may interact to form lethal damage.

3.3 Factors Influencing the Radiation Effect on Cells

The effect of radiation on a cell is governed by the 5Rs of radiobiology: repair, reassortment, repopulation, reoxygenation, and radiosensitivity. Repair, as described previously, can be either homologous or non-homologous end-joining repair. Reassortment is a result of the halt in the cell cycle phase due to activation of checkpoints. Thus, when a tissue is irradiated, some cells may be in the radioresistant S phase or in the radiosensitive G2–M phase, thus leading to only partial cell kill. However, after repair of the cells in the radioresistant phase, they progress to the radiosensitive G2 phase. Thus, delivery of a second fraction of radiation during this time will lead to death of the remaining cell clones. This forms the basis of fractionation. Repopulation is due to rapid growth of the cell clones that have survived the initial phase of radiation. This confers radioresistance during radiotherapy, and an additional dose is required to control these rapidly proliferating cells. Oxygen provides free radicals that are vital for the fixation of DNA damage. The relation between the 5Rs of radiobiology and the hallmarks of cancer are provided in Table 3.

The type of ionizing radiation also plays an important role. A radiation incident on a medium can be classified based on the amount of energy deposited in the medium. Linear energy transfer (LET) is defined as the average energy (in kiloelectron volts) given up by a charged particle traversing a distance of 1 μm. High LET radiations produce more ionizations per unit track. Examples of high LET radiations include neutrons, carbon ions, and alpha particles. Examples of low LET radiations include megavoltage photons, electrons, and cobalt-60 γ-rays. Another parameter used to describe the efficiency of radiation is the relative biological effectiveness (RBE). RBE is the ratio of the dose

Table 3 Correlation of the 5Rs of radiobiology with the hallmarks of cancer [18]

5Rs of radiobiology	Hallmarks of cancer
Repair	Growth factor self-sufficiency, evasion of apoptosis
Repopulation	Growth factor self-sufficiency, insensitivity to anti-growth factor signals, telomerase activation
Redistribution	Growth factor self-sufficiency, insensitivity to the anti-growth factor
Reoxygenation	Angiogenesis, growth factor self-sufficiency
Radiosensitivity	Growth factor self-sufficiency, evasion of apoptosis, insensitivity to anti-growth factor signals

of the reference radiation to that of the test radiation to produce the same biological effect. The reference radiation is usually 250 kVp X-rays or Co-60 rays. RBE is in the range of 2–10 for high RBE radiations. As LET increases, RBE also increases till it reaches 100 keV/mm. After this, the overkill effect sets in, which leads to wastage of the excess energy. Oxygen, as described above, is important for fixing DNA damage and is also a source of free radicals. Hence, the effect of oxygen can be determined by the oxygen enhancement ratio (OER). The OER is defined as the ratio of dose in hypoxia to that in air. The OER for X-rays is 3. There is a steep rise in the OER from 0.5 to 20 mmHg of oxygen followed by a plateau and a modest increase only. The opposite situation is when tumor hypoxia predominates. This leads to a rapid increase in radioresistance. Tumor hypoxia can be of two types, namely, acute and chronic. Acute hypoxia is due to the clogging of the blood vessels by tumor/blood cells or temporary collapse of the blood vessels. Chronic hypoxia is due the tumor outgrowing the vascular capacity of the feeder vessel. Thus, hypoxia can considerably increase tumor resistance to radiotherapy due to lack of oxygen and can also reduce the bioavailability of systemic drugs in the tumor due to poor vascular supply. The body's immune response also plays an important role in radiotherapy. Radiation upregulates antigen expression and cytokine release, thus mimicking a state of inflammation. This activates the antigen-presenting cells and sensitization of the T cells. This can lead to immune activation and control of distant metastatic tumor deposits. This effect is called the abscopal effect. With the advancements in immunotherapy, this is an upcoming frontier for research. The effect of radiotherapy can be potentiated with the use of systemic radiosensitizers like cisplatin and 5-fluorouracil. The role of cisplatin as a radiosensitizer is well-demonstrated in malignancies of the head, neck, and cervix. The main mechanism of radiosensitization is the formation of inter- and intra-strand adducts and the inhibition of DNA repair. The physical and biological properties of heat can be used to potentiate the effect of radiation. Temperatures from 39.5 to 43 °C have been used clinically. Hyperthermia coagulates and denaturizes the necessary proteins required for DNA repair. It also induces heat shock proteins (HSP-70), which upregulate the immune response. It has also been seen to cluster DNA damage so that the DSB changes increase [19, 20].

3.4 The Acute and Late Effects of Radiation

Radiobiology of the adverse effects following radiotherapy is critical for identification and appropriate management. Acute events are defined as effects that are seen within 90 days of starting radiotherapy; this is typically seen in skin and mucosal layers. Those beyond 90 days are termed as "late effects." The pathogenesis of acute events is a cascade of events following the start of radiotherapy. Irradiation of a normal tissue leads to vascular effects and inflammation; this, in turn, upregulates the functional stem cells in the basal layers. However, due to exposure to radiation, there is a destruction of these stem cells, which leads to hypoplasia and inadequate healing of the affected region. Inadequate healing may be complicated by a secondary infection. The reduced turnover of the functional cells is the primary cause of acute reactions, and, hence, the onset of the reaction typically correlates with the loss of residual functional cells and cell turnover of the affected region, e.g., 9 days after fractionated radiation to the mucosa [21]. The severity of acute reactions is based on the total dose of radiation, the duration of radiation, fractionation, and use of concurrent therapy. Late effects due to radiation are due to a complex interplay between the immune cells, fibroblasts, and vasculature. These are initiated with the loss of functional cells, which leads to compensatory proliferation of structural supporting cells such as fibroblasts. Radiation causes apoptosis of the endothelial cells, loss of smooth muscle, and damage to the surrounding veins and capillaries. Sclerosis and end arteritis occur in the arterioles, which may compromise blood supply. This causes proliferation of the defective vasculature, which lacks a precapillary sphincter, and is telangiectatic. This is prone to bleeding. Irradiation also causes differentiation of fibroblasts into fibrocytes with an increase in the production of transforming growth factor-β. This leads to additional fibrosis and collagen synthesis. The late effects are inversely dependent on the dose per fraction. Consequential reactions are the conversion of acute reactions into late reactions due to severity. This is typically seen in the skin and mucosa. An important concept in understanding the effect of radiation on a normal tissue is the functional arrangement of the irradiated organ. Each organ is made up of a functional subunit (FSU), and the arrangement is of prime importance while planning radiotherapy. Parallel organs are those that have their FSUs arranged in a parallel manner, whereas serial organs are those with FSUs arranged serially. This arrangement is not mutually exclusive of each other, but there is a degree of relativism between them. Relatively serial organs such as the spinal cord are sensitive to the maximum dose, whereas relatively parallel organs like the liver are sensitive to the mean dose. Mixed organs like the lungs, where the tracheobronchial tree is arranged serially and the parenchyma is arranged in a parallel manner, are sensitive to both the mean and maximum doses.

3.5 Fractionation

The intention behind fractionation is to reduce the number of hypoxic cells through reoxygenation, reduce the cells in the radioresistant phase by redistribution, improve oxygenation, and reduce hypoxia by opening of the blood vessels or shrinkage of the tumor. Fractionation also utilizes the recovery of the normal tissue between fractions, hence reducing reaction changes. The different types of fractionations are provided in Table 4. The main aim of modulating the dose per fraction and frequency is to widen the therapeutic window. While comparing different fractionation schedules, it is important to deliver the same biologically equivalent dose. Biologically equivalent dose (BED) = $nd\ [1 + d/(\alpha/\beta)]$. The BED must be calculated for acute- and late-reacting tissues when changing fractionation. The final dose must be reported in the equivalent dose in 2-Gy fractions (EQD2) (conventional). EQD2 = $nd\ [d + (\alpha/\beta)/2 + (\alpha/\beta)]$, where n is the number of fractions, d is the dose per fraction, and α/β is the dose where the linear cell kill is equal to the quadratic cell kill. The assumed α/β for acute- and late-reacting tissues are 10 and 3, respectively. The radiobiological basis of altered fractionation is provided in Table 5.

Table 4 Types of altered fractionations

Fractionation type	Dose per fraction (Gy)	No. of fractions	Duration of treatment
Conventional fractionation	1.8–2	Standard	Standard
Hyperfractionation	<1.8	More than one fraction per day	The same as conventional
Continuous hyperfractionated accelerated radiotherapy (CHART)	<1.8	Three fractions per day for 7 days a week	Reduced
Hypofractionation	>2	Reduced	The same or reduced

Table 5 Rationale of altered fractionation

Fractionation	Rationale	Effect on acute tissues	Effect on late tissues	Disadvantages
Conventional fractionation	To spare the normal tissue, reassortment, reoxygenation	Standard	Standard	Long treatment, chances of accelerated repopulation
Hyperfractionation	To reduce late toxicity	Standard or greater	Lower	Long treatment, chances of accelerated repopulation
CHART	To overcome accelerated repopulation	Greater	Standard	More acute toxicity, not suitable for all tumors and patients
Hypofractionation	Tumors with low α/β	Lower	Standard or higher	Propensity for higher late toxicity and need for high conformity

4 QUANTEC and Dose Constraints

Initial attempts to develop dose constraints consisted of correlating the total dose received by an organ with the percentage of risk of developing complications. Tolerance dose 5/5 represented the dose of radiation that could cause no more than 5% severe complications within 5 years of treatment. This was based on conventional fractionation. With the evolution of three-dimensional (3D) planning systems, volumetric data were available for analysis. This leads to volume-based dose constraints first developed by Emami [22]. This report consisted of minimal dose constraints for one-third, two-third, and the whole organ. There was still a need for a more robust volume-based constraint, taking into account other factors like chemotherapy. Thus, by 2010, robust data of volumetric dosimetry were accumulated, which led to qualitative analysis of normal tissue effects in the clinic (QUANTEC) [23]. The QUANTEC report consisted of constraints for 16 organs; robust follow-up data with the impact of confounding factors like chemotherapy were addressed. The concise recommendations from the QUANTEC report are presented in Tables 6 and 7.

Table 6 QUANTEC recommendations

Organ	Volume	End point	Constraint	Toxicity rate
Brain	Whole organ	Symptomatic necrosis	<60 Gy	<3%
			72 Gy	5%
			90 Gy	10%
Brain stem	Whole organ	Permanent cranial neuropathy or necrosis	<54 Gy	<5%
			<64 Gy	<5%
			D1–10 mL ≤59 Gy	<5%
Optic nerve/chiasm	Whole organ	Optic neuropathy	<55 Gy	<3%
			55–60 Gy	3–7%
			>60 Gy	>7–20%
Spinal cord	Partial organ	Myelopathy	50 Gy	0.2%
			60 Gy	6%
			69 Gy	50%
Cochlea	Whole organ	Sensory neural hearing loss	Mean dose ≤45 Gy	<30%
Parotid bilateral	Whole organ	25% Reduction in salivary function	Mean dose <25%	<20%
			Mean dose <39 Gy	<50%
Parotid unilateral	Whole organ	25% Reduction in salivary function	Mean dose <20 Gy	<20%
Pharyngeal constrictors	Whole organ	Symptomatic dysphagia and aspiration	Mean dose <50 Gy	<20%
Larynx	Whole organ	Vocal dysfunction	<66 Gy	<20%
		Aspiration	Mean dose <50 Gy	<30%
		Edema	Mean dose <44 Gy	<20%
		Edema	V50 <27%	<20%
Lungs	Whole organ	Symptomatic pneumonitis	V20 ≤30%	<20%
			Mean dose 7 Gy	5%
			Mean dose 13 Gy	10%
			Mean dose 20 Gy	20%
			Mean dose 24 Gy	30%
			Mean dose 27 Gy	40%
Esophagus	Whole organ	Grade 3 or higher esophagitis	Mean dose <34 Gy	5–20%
		Grade 2 or higher esophagitis	V35 <50%	<30%
		Grade 2 or higher esophagitis	V50 <40%	<30%
		Grade 2 or higher esophagitis	V70 <20%	<30%
Heart	Pericardium	Pericarditis	Mean dose <26 Gy	<15%
	Pericardium	Pericarditis	V30 <46 Gy	<15%
	Whole organ	Long-term cardiac mortality	V25 <10%	<1%
Liver	Whole liver—GTV	Classic Radiation Induced Liver Disease (RILD)	Mean dose <30–32 Gy	<5%
			Mean dose <42 Gy	<50%
			Mean dose <28 Gy	<5%
			Mean dose <36 Gy	<50%
Kidneys	Bilateral whole kidney	Clinically relevant renal dysfunction	Mean dose <15–18 Gy	<5%
			Mean dose <28 Gy	<50%
			V12 <55%	<5%
			V20 <32%	<5%
			V28 <20%	<5%

Table 6 (continued)

Organ	Volume	End point	Constraint	Toxicity rate
Stomach	Whole organ	Ulceration	<45 Gy	<7%
Small bowel	Individual loops	Grade 3 or higher acute toxicity	V15 <120 mL	<10%
	Entire peritoneal cavity	Grade 3 or higher acute toxicity	V45 <195 mL	<10%
Rectum	Whole organ	Grade 3 or higher late toxicity	V50 <50%	<10%
			V60 <35%	<10%
			V65 <25%	<10%
			V70 <20%	<10%
			V75 <15%	<10%
Bladder	Whole organ	Grade 3 or higher late Radiation Therapy Oncology Group (RTOG) toxicity	<65 Gy	<6%
		Grade 3 or higher late RTOG toxicity	V65 ≤50%	
			V70 ≤35%	
			V75 ≤25%	
			V80 ≤15%	
Penile bulb	Whole organ	Severe erectile dysfunction	Mean dose to 95% of the gland <50 Gy	<35%
			D90 <50 Gy	<35%
			D60–70 <70 Gy	<35%

Table 7 QUANTEC dose constraints for SBRT (single fraction)

Organ	Volume	End point	Constraint	Toxicity rate
Brain	Whole organ	Symptomatic necrosis	V12 <5–10 cc	<20%
Brain stem	Whole organ		<12.5 Gy	<5%
Optic nerve/chiasm	Whole organ		<12 Gy	<10%
Spinal cord	Partial organ	Myelopathy	13 Gy	1%
Cochlea	Whole organ	Sensory neural hearing loss	<14 Gy	<25%
Liver/hepatocellular carcinoma (HCC) (three fractions)	Whole liver—GTV	RILD	Mean <13 Gy	<5%
Liver/metastases (three fractions)	Whole liver—GTV	RILD	Mean <15 Gy	<5%
Liver (three fractions)	>700 cc	RILD	<15 Gy	<5%

5 Radiobiology of Brachytherapy

Unlike external beam radiotherapy, the dose distribution attained in brachytherapy is extremely unique. The region near the source receives an extremely high dose, whereas the region away from the source receives a much lesser dose. The dose distribution in brachytherapy is governed by the inverse square law. Thus, dose heterogeneity must be accepted with brachytherapy. This can be used as an advantage when we position the radioactive source within the tumor, thus escalating the dose to the tumor. The radiobiology of low-dose-rate brachytherapy differs considerably from that of high-dose-rate. With LDR brachytherapy, simultaneous repair occurs, which is beneficial to normal tissues, and, then, repopulation of the surviving cells occurs. Reoxygenation that occurs during prolonged LDR treatment increases the radiosensitivity of the surviving clones. Reassortment from the radioresistant phase to the radiosensitive phase also contributes to increased sensitivity. A phenomenon called the inversed dose rate effect can also occur when the cell progresses during radiation till the G2 phase where it undergoes death due to the increased radiosensitivity of the G2 phase.

6 Radiation Modifiers

The effect of radiation can be enhanced by the use of physical and chemical modifiers. Chemical modifiers include hypoxic sensitizers. Compounds with high electron affinity produce free radicals, thus sensitizing hypoxic cells to radiation. The classical example is misonidazole, which is used in many clinical trials. Perfluorocarbons are also other agents, which work on a similar mechanism. Cytotoxic agents such as actinomycin D, doxorubicin, cisplatin, etc. have shown to be efficient radiosensitizers. Radiotherapy increases the expression of epithelial growth factor receptors (EGFRs) on the cell surface; therefore, when EGFR blockers are added to radiotherapy, the effect of radiation may be potentiated. It has shown to improve locoregional control in locally advanced squamous cell carcinomas. Apart from potentiating the effect of radiation, there are some chemical compounds that act as radioprotectors, such as amifostine, which acts as a free radical scavenger. It has been used to reduce the incidence of xerostomia in patients with head and neck cancer treated with radiotherapy. Hypoxia is a known factor that has contributed to radioresistance. Thus, hyperbaric oxygen, carbogen, and nicotinamide have been used to overcome both acute and chronic hypoxia. Erythropoietin increases red blood cell production, thus increasing the oxygen-carrying capacity. Indirectly, it helps overcome hypoxia. Hyperthermia is also a useful method to mitigate radioresistance by selectively killing hypoxic, acidic, and nutritionally deprived cells.

7 The Physics of Radiotherapy

7.1 The Basic Physics of Radiotherapy

Having understood the physical and biological aspects of how radiations interact with matter, the next important aspect in physics that requires a thorough understanding is the photon beam, linear accelerator, and the basic concepts of the various processes involved in radiotherapy. Some important definitions and concepts are provided in Tables 8 and 9.

The setup of a patient for treatment is of two types, source-to-skin distance (SSD) and source-to-axis distance (SAD). In the SSD technique, the patient is set at the isocenter of the machine, 80 cm for cobalt and 100 cm for linear accelerators. Each field has to be set individually with verification of the field size on the skin. In the SAD technique, the isocenter is ideally placed at the center of the tumor and the gantry rotates around the isocenter. Thus, the patient requires to be setup for only one field. The field size seen on the skin with the SAD technique is essentially smaller than the field size at the isocenter.

Table 8 Important terms and definitions

Term	Definition
Dose	Amount of mass deposited per unit mass of material. The SI unit is Gray; 1 Gy = 1 J/kg
KERMA	Kinetic energy released in a medium expressed in Joules per kilogram
Percentage depth dose (PDD)	Ratio of the dose at a depth D_d to the maximum dose D_m along the central axis of the beam, expressed in percentage
Buildup region	Region between the incident surface and the region of maximum dose (D_{max})
D_{max}	Depth of the maximum dose also called the reference point
Field size	Distance from the field edge at the 50% isodose line with 100% normalization at the central axis of the beam
Flatness	Deviation of the dose level across the central axis of the beam
Symmetry	Deviation in the dose level of symmetric points on either side of the central axis
Penumbra	Region covered by the 80–20% isodose line
Half-value layer	Thickness of the material required to reduce the intensity of the incident beam to 50% of its original value
Isocenter	Point in space around which the axes of the gantry, collimator, and couch rotate

Table 9 Effects of various parameters on a photon beam

Parameters	Effect on a beam
Energy	Increase in PDD with increase in energy
	Surface dose reduces with increase in energy (skin sparing)
	Increase in Half Value Layer (HVL) with increase in energy
	Lesser scatter with increase in energy
Field size	PDD increases with field size
	Surface dose increases with field size
	Beam output increases with increase in field size
Penumbra	Increases as depth increases
	Increases with increase in field size
	Increases with increase in source-to-skin distance (SSD)
	Increases with the size of the source

Simulation in radiotherapy is a process by which the patient's intended treatment position is replicated with appropriate immobilization devices and an image is acquired. The acquired image can be in the form of two-dimensional (2D) X-rays, computed tomography (CT) scanning, magnetic resonance imaging (MRI), or positron emission tomography (PET) scanning. Care must be taken to simulate the treatment conditions such as identical bladder filling, rectal distention, and immobilization. When 3D images are acquired, it is advisable to take thin slices because the quality of reconstruction is better with thin slices. The acquired images are then imported into the planning and contouring station.

Treatment in radiation oncology is volume-based. Thus, a proper understanding of the concepts of volume is essential for proper planning and treatment. The International Commission on Radiation Units and Measurements (ICRU) has developed recommendations for uniform reporting of treatment parameters. The recommended volumes as per the ICRU are provided in Table 10.

As per the ICRU 83 report, it is recommended to report the $D_{near\text{-}min}$ or $D_{98\%}$ and the $D_{near\text{-}max}$ or $D_{2\%}$ for tumors, the mean dose for parallel organs at risk (OARs), and the maximum dose for serial organs. Other parameters recommended are homogeneity index (HI = (D2% − D98%)/D50%) and the conformity index (CI).

Table 10 Volumes as per ICRU

Gross tumor volume (GTV)	Volume that contains gross palpable or visible/demonstrable extent and location of malignant growth
Clinical target volume (CTV)	Region around the tumor where there is subclinical involvement by individual malignant cells, small cell clusters, or micro-extensions, which cannot be detected by staging procedures
Planning target volume (PTV)	Volume that encloses the GTV and CTV, which accounts for uncertainties in organ motion and setup uncertainties
Treated volume (TV)	Volume enclosed by an isodose surface, the value of which is the minimum target-absorbed dose
Irradiated volume (IV)	Volume that receives an absorbed dose, which is considered significant in relation to tissue tolerance (e.g., 50%) of the specified target-absorbed dose
Internal target volume (ITV)	Volume to account for variations in size, shape, and position of the CTV in relation to anatomical reference points
Organ at risk (OAR)	Normal tissue at risk of radiation-induced morbidity
Planning organ at risk volume (PRV)	Volume to account for variations in OAR motion and setup uncertainty

8 External Beam Radiography

External beam radiotherapy is delivered with the help of telecobalt or linear accelerators. The construction of a telecobalt unit consists of a radioactive telecobalt source housed in a shielded gantry. The cobalt source is a cylindrical double-walled sealed source of 3-cm diameter and 5-cm height. The half-life of Co-60 is 5.2 years. The source is kept in a shielded gantry, and, on initiation, it is moved to the gantry head with the help of a pneumatic system. The gantry contains collimators, which help in determining the field size. The maximum field size is 35 × 35 cm^2 at 80-cm SSD. An emergency T-bar is provided, which can be used to push the source in case of mechanical failure. The unit is isocentrically mounted and can rotate 360° along the isocenter. In contrast, a linear accelerator consists of a target with a high atomic number, such as tungsten, which produces X-rays by bremsstrahlung interactions. The electrons are produced by thermoluminescence from an electron gun. They are accelerated with the help of microwaves produced by a magnetron (<10 MV) or a klystron. These microwaves accelerate the electrons in the wave guide. Based on the energy of the photons, there may be bending magnets before the electrons strike the target. The target is of transmission type, which is placed on a carrousel with a scattering foil when electrons are required for treatment. A flattening filter is placed below the target to harden the beam and to produce a uniform intensity across the beam profile. Newer accelerators have the provision for flattening the filter-free option, which leads to increased output and an inhomogeneous beam profile. Monitor chambers are placed below the flattening filter to monitor the amount of radiation exiting the machine and also to check for symmetry. Collimators are present below along with Multileaf Collimator (MLC) for shaping of the treatment field. A modification of the modern linear accelerator is TomoTherapy. It comprises a circular ring CT gantry mounted on an isocenter. It is a single-energy (6-MV) accelerator, which produces a fan-shaped beam. Thus, the volume of interest is treated slice by slice with continuous movement of the couch. The MLC in TomoTherapy is binary and consists of only an on or off position. Verification of the target position can be done before treatment with the help of 2D orthogonal X-rays [electronic portal imaging devices (EPIDs)], a cone or a mega-voltage (MV) fan beam, and a CT scanner. The process of verification of the target before treatment and then appropriately matching the treatment volume with the help of onboard imaging is called IGRT.

The treatment fields in radiotherapy have evolved from conventional open fields to highly conformal intensity-modulated fields. Conventional radiotherapy fields consist of open fields with minimal sparing of the normal tissue. Custom-made blocks had to be developed to shape the fields appropriately to spare the normal tissue. With the advent of MLCs, the shaping of multiple fields has become easy, thus leading to the development of 3D conformal radiotherapy. However, optimal sparing of OARs was still not achievable. There was still a high-dose region at the field junctions and dose inhomogeneity over irregular surfaces. Intensity-modulated radiotherapy consists of dividing the entire field into multiple beamlets and modulation of the photon intensity across each beamlet with the help of MLC motion. Thus, an inhomogeneous field can be developed, which can be adapted to clinical requirements (Fig. 1). IMRT initially started with a static field step and shoot IMRT, but, with further advancements, the MLC motion could be synchronized with the motion of the gantry, thus leading to the development of volumetric modulated arc therapy (VMAT). This led to shorter treatment times and highly conformal treatment plans.

For stereotactic radiotherapy (SRT), more sophisticated linear accelerators and cobalt units have been developed, namely, the LINAC radiosurgery unit and the gamma stereo-

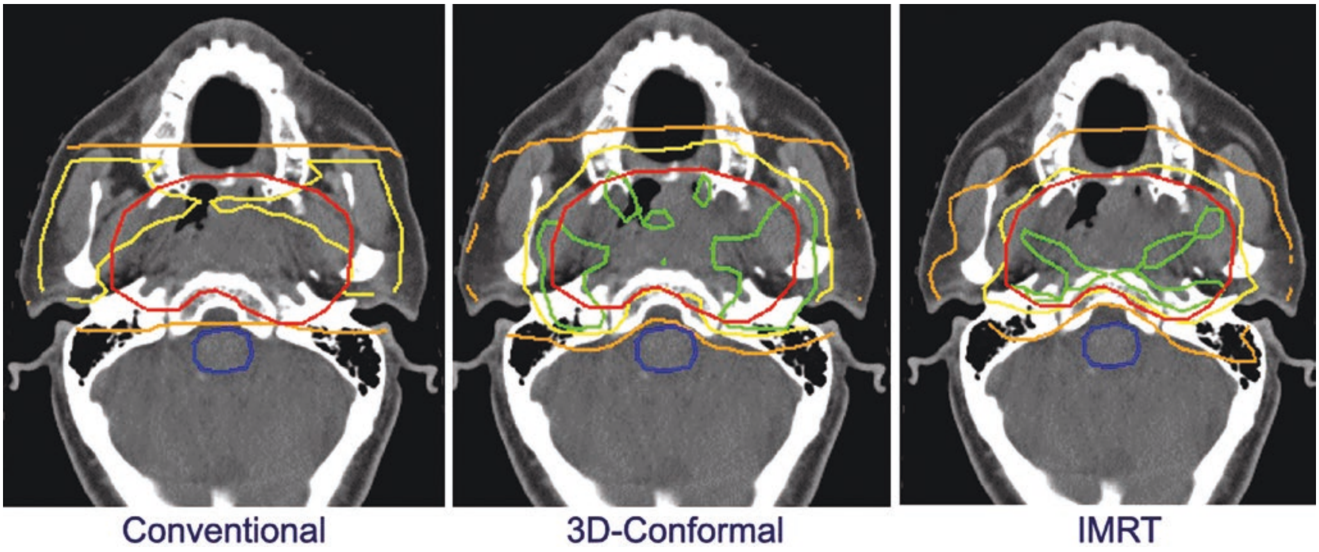

Fig. 1 Dose distribution comparing conventional 3D-conformal technique and intensity-modulated radiotherapy plans

tactic radiosurgery (SRS) unit. The gamma radiosurgery unit consists of 30–200 Co-60 sources arranged in a hemispherical pattern focusing on an isocenter. The source-to-focus distance is 40 cm. The LINAC radiosurgery unit consists of a linear accelerator mounted on a mobile gantry. There is a circular tertiary collimator that opens to form circular fields at 77 cm from the target.

Recently, there has been growing interest in the use of charged particles for delivering external beam radiation therapy. The greatest physical advantage of particle therapy (e.g., protons) over conventional X-ray therapy is the sharp fall-off of the radiation dose beyond the target tissue with particles compared to X-rays, thus allowing better sparing of the normal tissues. Heavy particles like carbon ions have an added biological advantage over X-rays. Heavy ions have a greater efficiency in cell kill (RBE) compared to X-rays, and they remain efficacious even in the absence of oxygen (OER).

9 Brachytherapy

The term "brachytherapy" originates from "brachy," meaning short, hence implying short-distance therapy. In brachytherapy, the radioactive source is kept within or in the vicinity of the tumor. The advantages of brachytherapy over external beam radiotherapy are that the dose fall-off with increasing distance is extremely steep. Photons produced by brachytherapy sources have extremely low energies and are attenuated extremely easily. The inhomogeneous dose profile produced by brachytherapy can be used to escalate the dose to the tumor while sparing the OARs. Historically, radium sources were used for brachytherapy, which involved inadvertent exposure of the oncologist and also required extensive shielding. With the development of artificial radioactive sources like cesium and iridium, the use of radium has declined. Development of remote after-loading techniques has reduced the radiation exposure of physicians considerably. Unlike external beam radiotherapy, the dose prescribed for brachytherapy has been developed from the amount of the radioactive source and the duration of the treatment. This was relevant in the radium era, but, with the development of artificial isotopes with varying dose rates, the calculations based on radium are not reliable. Hence, a new term, "Total Reference Air Kerma (TRAK)," was developed. It is the integral of the reference air kinetic energy released in a medium (KERMA) over the treatment duration for all source positions. The absorbed dose at any point is directly proportional to TRAK. Conversion of radium equivalent hours (mgHr) to TRAK uses a constant of 7.227 mGy. Systems in brachytherapy are a set of rules for implanting and prescribing radiation. There are two main methods of brachytherapy, i.e., interstitial and intracavitary brachytherapy. The commonly followed system for interstitial brachytherapy is the Paris system. It describes the ideal geometry of an implant such as in squares or triangles to obtain an ideal dose distribution. A concept introduced is the basal dose rate, which is the dose rate at the center of the treated volume at the central plane. The reference dose rate is 85% of the basal dose rate for which the implant is prescribed. Treatment volume is the volume enclosed by the 85% isodose line. The hyperdose sleeve is the region covered by the 170% isodose line. Interstitial brachytherapy is widely used for many cancers like head and neck, soft tissue sarcoma, and breast.

Intracavitary brachytherapy for carcinoma of the cervix is one of the most commonly used indications of brachytherapy. It has transitioned from X-ray-based 2D planning and point-based prescription to 3D volumetric image-

Table 11 Dose points used in carcinoma of the cervix

Points	Description
POINT A (Original Manchester 1938)	It is 2 cm lateral to the central canal of the uterus and 2 cm up from the mucous membrane of the lateral fornix in the axis of the uterus
Revised Manchester point A (1953)	It is 2 cm superior from the lower end of the ventral radium tube and 2 cm lateral from the uterine canal
ABS point A	Draw a line connecting the middle of the vaginal source on the anterior–posterior (AP) radiograph and move 2 cm plus the radius of the ovoid superiorly along the tandem from the intersection of this line with the intrauterine source line and then 2 cm lateral on either side of the tandem
Point B	At the same level of point A but 5 cm from the midline
Point P	The same plane as point A but 6 cm lateral to the midline

Table 12 ICRU 89 volumes

GTVinitial	Gross macroscopic disease at presentation
GTVres	Macroscopic residual disease after 45–50 Gy of External Beam Radiation Therapy (EBRT)
High-risk CTV	Whole cervix, residual GTV, residual pathological tissue
Intermediate-risk CTV	GTVint, HR CTV + margins to account for the microscopic residual disease in the region outside the HR CTV
Low-risk CTV	Entire cervix, body of uterus, parametrium, and upper one-third of the vagina

guided brachytherapy prescription. The classical point A described in the Manchester system has evolved over time. Table 11 provides the various dose points used in brachytherapy of carcinoma of the cervix. The current Group European de Curitherapie-European Society for Radiotherapy & Oncology (GEC-ESTRO) and ICRU 89 reports recommend volumetric reporting of brachytherapy dose prescription. Table 12 highlights the various volumes for reporting according to ICRU 89.

10 Special Techniques and Technologies in Radiation Oncology

10.1 Total Skin Electron Therapy (TSET)

This technique of external beam radiation therapy is used for treatment of the entire skin surface or a part of it. The most common indication is for treatment of mycosis fungoides. The six-field, modified Stanford technique is used most frequently. This technique uses 4–6-MeV electrons with the patient standing in predefined positions at an extended SSD of 300–400 cm. Two different beam angles are used to adequately encompass the entire body surface. A beam spoiler is placed in the beam path close to the body surface in order to increase the skin dose. Areas that are underdosed (the scalp, sole, perineum, etc.) may require an additional boost dose to prevent underdosing. A detailed technical description is available in the American Association of Physicists in Medicine (AAPM) Report No. 23.

10.2 Stereotactic Radiosurgery (SRS)/Stereotactic Radiotherapy (SRT)

These are techniques to administer precise, high-dose radiation that tightly conforms to the target. This technique is based on the fact that radiation tolerance is volume-dependent. The term “radiosurgery” is used when the treatment involves a single fraction regimen, whereas the term “radiotherapy” is used when multiple fractions are delivered. The first stereotactic radiosurgery equipment was designed by Leksell in 1967 where multiple cobalt sources were placed in a hemispherical array. A LINAC-based radiosurgery model was designed in 1980; it consisted of a linear accelerator mounted on a robotic arm that could move in six axes. The image-processing system had two orthogonal X-rays to track the target. Clinically, these techniques are used in the management of benign conditions like trigeminal neuralgia, Arterio Venous Malformation (AVM), schwannoma and also for malignant lesions like metastasis.

10.3 Stereotactic Body Radiotherapy (SBRT)

It is the use of image-guided high-dose radiotherapy with tumor-ablative intent and the maximum number of fractions not exceeding five. This is used in tumors that have an extremely low α/β such as prostate. It is also currently employed in treating extremely early tumors that have small treatment volume and also in oligometastatic disease. There are specific American College of Radiology/Americal Society for Therapeutic Radiology & Oncology (ACR/ASTRO) guidelines for those who wish to practice SBRT routinely. High precision is required in the SBRT; hence, adequate immobilization and target motion management with appropriate gating methods, as in the lung or deep inspiratory breath hold as in the pancreas, are necessary. Currently, SBRT is making inroads into sites like the liver, lungs, pancreas, and oligometastatic sites.

10.4 Total Body Irradiation (TBI)

This is a highly novel technique of irradiating the entire body to a homogeneous dose. The most important indication currently is a conditioning method before stem cell transplantation. Based on the total dose of radiation used, TBI can be classified as either myeloablative (e.g., 12 Gy) or non-myeloablative (e.g., 2 Gy). TBI has a dual effect in the form of cytotoxicity and immune modulation and remains effective against malignant cells located both at sanctuary and non-sanctuary sites. The most fatal and dose-limiting toxicity of TBI is pulmonary toxicity. There are higher rates of pulmonary toxicity, with those having underlying pulmonary dysfunction, busulfan, and cyclophosphamide-based conditioning regimen. Lowering the dose rate to <0.025 Gy/min has been shown to reduce pulmonary toxicity along with reduction in the total dose. A detailed description of the physical aspect of TBI is provided in AAPM TG 17.

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Systemic Treatment of Cancer

Shona Nag and Sudeep Gupta

Abbreviations

ADC	Antibody drug conjugate
ADCC	Antigen-dependent cellular cytotoxicity
AML	Acute myeloid leukemia
B-ALL	B-cell acute lymphocytic leukemia
B-CLL	B-cell chronic lymphocytic leukemia
CAR-T	Chimeric antigen receptor T cell
CDCC	Complement-dependent cytotoxicity
CML	Chronic myelogenous leukemia
DHT	Dihydrotestosterone
ER	Estrogen receptor
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
NHL	Non-Hodgkin's lymphoma
PR	Progesterone receptor

1 Introduction

Cancer is a systemic disease. This implies that although the manifestation of a tumor may be local, i.e., a breast lump or a rectal mass, if treated only with local therapy such as surgical removal, then there is a reasonable chance of metastasis developing in the future. The likely explanation for the development of metastasis is the presence of residual microscopic disease, which grows over time to present as widespread metastatic disease. The treatment that addresses this microscopic disease and delays or prevents a relapse is referred to as "systemic treatment" for cancer. It is often referred to as adjuvant cancer treatment, as it follows the initial treatment of a tumor, which could be in the form of a surgery or local radiation therapy. The goal of this treatment is cure. Systemic treatment can also be administered to cancers that are already advanced or metastatic. In this setting, it is called palliative therapy, and the major goals are symptom control and prolongation of life.

2 The History of Systemic Treatment

There are three observations that have contributed to modern cancer systemic therapy as we know it today. The first was made by Paul Ehrlich in the nineteenth century who coined the term "chemotherapy" for compounds or magic bullets that demonstrated activity against parasites, causing the maximum toxicity to the pathogen and least to the host [1, 2]. He is considered the father of chemotherapy.

The second observation was made in 1896 by an English surgeon, George Beatson, who performed an oophorectomy in a 33-year-old woman with advanced breast cancer who went on to live for 4 years after the operation [3]. He performed other similar surgeries and concluded that women with breast cancer benefitted from this approach, providing that they were carefully selected [4]. This observation formed the foundation of hormonal therapy for breast cancer as it is practiced today.

The third observation took place during World War I, when the toxic effects of mustard gas used for combat resulted in hypoplasia of the bone marrow and lymph nodes. This agent was then used to treat a patient with non-Hodgkin's lymphoma (NHL) in 1942 and, subsequently, showed dramatic regressions in lymphomas, thus generating considerable enthusiasm in the pharmacology of cancer.

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3 Types of Cancer Systemic Therapies

Systemic cancer treatment can be categorized into four different types

1. Conventional cancer chemotherapy—targets the DNA structure of the cancer cell
2. Hormonal therapy—attacks the biochemical pathways underlying the estrogen and androgen functions
3. Targeted therapy (also known as biological therapy)—a key pathway or process driving the growth of a particular tumor is interrupted
4. Immunotherapy—harnesses the body's own immune system to fight the cancer cells

Table 1 shows the categories of systemic therapies available and in clinical use at present.

Table 1 Systemic therapies in current clinical use

Systemic therapy	Class	Examples
A. Cytotoxic chemotherapy	Antifolates	Methotrexate
	5-Fluoropyrimidines	5-Fluorouracil
	Cytidine analogues	Cytosine arabinoside
	Purine antimetabolites	6-Mercaptopurine
	Hydroxyurea	
	Antimitotic drugs	Vincristine, paclitaxel
	Alkylating agents	Cyclophosphamide
	Platinum analogues	Cisplatin, carboplatin
	Antitumor antibiotics	Bleomycin
	Topoisomerase 1 inhibitors	Topotecan
	Topoisomerase 2 inhibitors	
	Anthracyclines	Doxorubicin
	Epipodophyllotoxins	Etoposide
	Asparaginase	L-Asparaginase
B. Hormonal therapy	Selective estrogen receptor modulators	Tamoxifen
	Antiestrogens	Fulvestrant
	Aromatase inhibitors	Letrozole
	LHRH agonists	Goserelin
	Antiandrogens	Bicalutamide
	Steroidogenesis inhibitors	Abiraterone acetate
C. Molecular targeted therapies	Proteosome inhibitors	Bortezomib
	Histone deacetylase inhibitors	Vorinostat
	Differentiating agents	ATRA
	Arsenic trioxide	
	Monoclonal antibodies	Rituximab
	Angiogenesis inhibitors	Bevacizumab
	EGFR (epidermal growth factor receptor) inhibitors	Gefitinib
	Her2 inhibitors	Trastuzumab
	Molecular targeted drugs	Imatinib
D. Immunotherapy	Cytokine therapy	Interferons
	Cancer vaccines	HSP/peptide vaccine
	Adoptive cellular therapies	CAR-T cell therapy
	Checkpoint inhibitors	Pembrolizumab

4 Settings for Cancer Systemic Treatment

Primary or Induction Therapy: This is the first treatment for patients who present with advanced cancers, for which there is no other alternative therapy, e.g., chemotherapy for acute leukemias and chemotherapy for germ cell tumors.

Neoadjuvant Therapy: This is the use of systemic treatment, usually chemotherapy, administered before a definitive local treatment such as a surgery or radiotherapy in order to shrink the tumor, thus allowing for higher rates of surgical resection and eradication of micrometastasis, e.g., chemotherapy for osteogenic sarcoma and for breast cancer.

Adjuvant Therapy: This is the use of systemic therapy after definitive local treatment to eradicate micrometastasis in order to improve cure rates, e.g., hormonal therapy for breast cancer and colon cancers and targeted therapy for ovarian cancer.

Palliative Therapy: This is the use of systemic therapy for advanced tumors in order to mitigate symptoms and prolong survival, e.g., targeted therapies and immunotherapy for non-small cell lung cancer and renal cell carcinoma.

Concurrent Therapy: This is administered along with radiation to improve response rates and survival, e.g., concurrent chemotherapy administered during radiation for cervical cancer.

Table 2 shows the tumors and the main clinical settings where chemotherapy has had the largest impact.

This chapter will describe the principles underlying each type of treatment and highlight the key concepts supporting their use.

Table 2 Clinical settings in which systemic therapy has the largest impact

A. In the adjuvant setting after surgery
Breast cancer
Colorectal cancer
Gastric cancer
Ovarian cancer
Pancreatic cancer
Testicular cancer
B. In the neoadjuvant setting for locally advanced disease
Osteogenic sarcoma
Breast cancer
Bladder cancer
Head and neck cancer
Gastroesophageal cancer
Rectal cancer
C. In the advanced or metastatic setting
Non-small cell lung cancer
Breast cancer
Pancreatic cancer
Colorectal cancer
Nasopharyngeal cancer
Prostate cancer
D. As the primary treatment modality
Acute leukemia
Non-Hodgkin's lymphoma
Small cell lung cancer
Myeloma
Embryonal rhabdomyosarcoma
Germ cell cancer

5 The Principles of Chemotherapy

5.1 Cancer Cellular Kinetics

It is important to understand the distinct growth patterns of normal and tumor cells. Both share the property of having two types of cells: those that actively divide and progress through the cell cycle, resulting in growth, and those in the resting or dormant phase. Some of these resting cancer cells are the cancer stem cells responsible for relapses and are difficult to eliminate as they are highly resistant to conventional systemic therapies.

Various model systems have been developed to describe the growth pattern of cancer cells. Skipper et al. [5] used murine leukemia L1210 cells as their first experimental model system in order to describe cancer cell kinetics. Based on their findings with this model, the cytotoxicity of cancer chemotherapy followed a logarithmic or exponential cell kill or first-order kinetics. What this means is that a given dose of a chemotherapeutic drug kills a constant proportion or a fraction of a cancer cell population and not a constant number. Therefore, every time a drug is administered, it destroys a fixed percentage of cells rather than a fixed number. This phenomenon is also referred to as log kill. For example, if a particular cancer drug has a 3-log kill, then it will reduce the cancer cell population from 10^{12} to 10^9 cells. Similarly, a tumor burden of 10^5 cells would come down to 10^2 cells with the same treatment. This model also established an important caveat for chemotherapy—cure with chemotherapy was inversely proportional to the cell number or tumor burden. This model also assumes that growth fraction, i.e., the proportion of cells in a tumor, which are dividing, remains constant.

The fractional kill hypothesis has important clinical implications (Fig. 1). It appears that the chances of cure are the highest when tumor burden is low, e.g., after surgery. For the tumor to be clinically detectable, it has to grow to a size of 10^9 cells. In this case, each session of chemotherapy provides a cell kill of 2 logs, but the problem is that the time interval between the administration of two chemotherapies allows tumor regrowth of 1 log. Often, resistance develops with continuation of chemotherapeutic treatment.

However, human solid tumors do not follow first-order kinetics. The data for solid tumors support the Gompertzian model of growth. The main difference between the exponential and the Gompertzian model is that the growth fraction in the Gompertzian model is not constant but decreases with time. In this model, it is stipulated that the growth fraction of the tumor is the highest when the tumor reaches 37% of its maximum size. Thereafter, the growth fraction slows down and plateaus before decreasing. The possible explanation for this is the lack of oxygen, blood supply, and nutrients to which the tumor has access as its size grows. The clinical implication is that the response of a solid tumor to chemotherapy depends on which part of the growth phase it has been diagnosed at—making smaller tumors more chemosensitive as they have a larger growth fraction. However, regrowth would also be faster between chemotherapy cycles for smaller tumors, thus underscoring the fact that size alone is not the only determinant to administering adjuvant chemotherapy (Fig. 2).

5.2 Rationale for Chemotherapeutic Combinations

It is well-established that single chemotherapeutic drugs are unable to cure cancer. The early combination therapies were not very effective due to a paucity of available active agents. Later, this problem was overcome and a number of rational chemotherapeutic combination regimens were developed for several tumor types. The advantages of using chemotherapeutic combinations are manifold:

1. Each chemotherapeutic agent can be used in full doses within the toxicity range, leading to the maximum cell kill of the tumor.

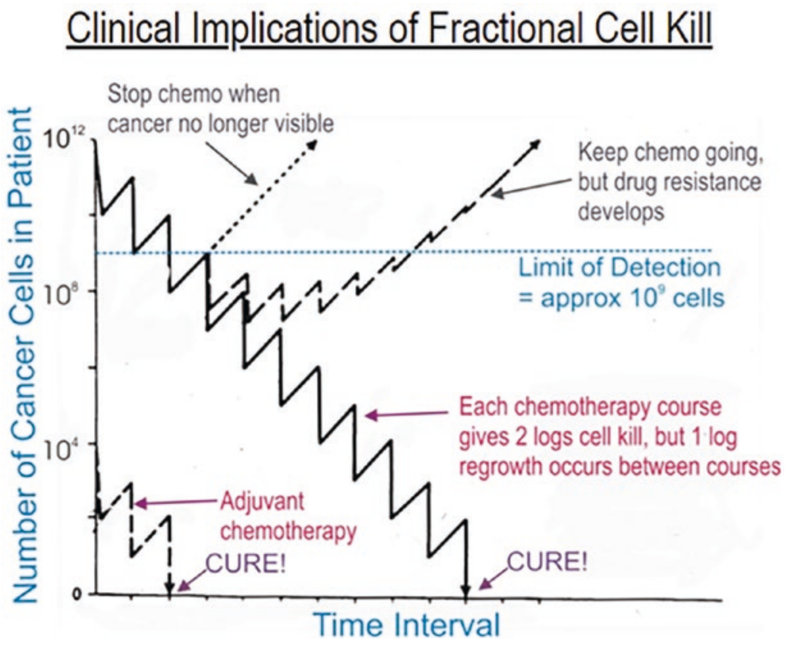
Clinical Implications of Fractional Cell Kill
Number of Cancer Cells in Patient
10^{12}
10^{8}
10^{4}
0
Stop chemo when cancer no longer visible
Keep chemo going, but drug resistance develops
Limit of Detection = approx 10^{9} cells
Each chemotherapy course gives 2 logs cell kill, but 1 log regrowth occurs between courses
Adjuvant chemotherapy
CURE!
CURE!
Time Interval

Fig. 1 The clinical implications of the fractional cell kill hypothesis

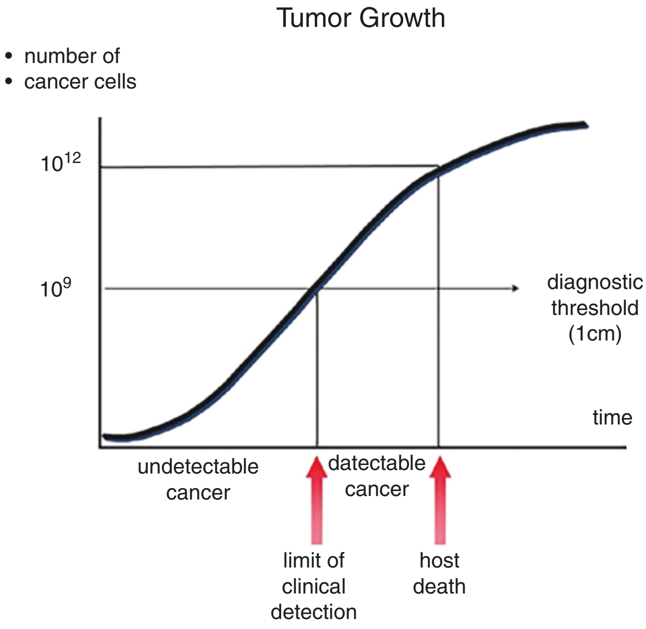
Tumor Growth
• number of
• cancer cells
10^{12}
10^{9}
diagnostic threshold (1cm)
time
undetectable cancer
datectable cancer
limit of clinical detection
host death

Fig. 2 The Gompertzian model for solid tumors

2. As thetumor is genetically heterogeneous, the use of combination chemotherapy allows drug and tumor cell interaction at several levels.
3. Combination chemotherapy has the potential to delay or prevent the development of resistance.

The selection of different chemotherapeutic drugs to be used in combination also follows certain principles. First, only drugs that have been proven to be effective in treating that particular tumor type are to be included in combination with each other. Drugs that are likely to produce complete responses in at least a fraction of the patients are preferable to those that produce partial responses. Lastly, drugs with nonoverlapping toxicities are selected for combination therapies.

Other important aspects while choosing chemotherapeutic drug combinations are as follows

1. A good understanding of the biochemistry and pharmacokinetics and interactions between the drugs in the combination chosen.
2. Arbitrary reduction of doses of a drug in a combination may dramatically compromise the efficacy of the combination.
3. The interval between two doses of chemotherapy is simply to allow the bone marrow of the host to recover for the next dose to be administered and is usually 3 weeks. This interval can be shortened by the use of growth factors.
4. The duration of chemotherapy administration depends on the clinical situation. It can vary between 4 and 6 months in the adjuvant setting. For metastatic disease, chemotherapy is usually continued until disease progression or unacceptable toxicity.
5. It is vital to determine the therapeutic index of the drug. This is defined as the comparison between the amount of drug required for the therapeutic effect and the amount required to cause toxicity. Really useful drugs have a large therapeutic index. Unfortunately, most chemotherapeutic drugs have a narrow therapeutic window and toxicities have to be kept in mind while combining them.

5.3 The Concept of Dose Intensity

Effective dosing of chemotherapy is critical to achieve cure. The dose–response curve in most biological systems is sigmoidal, as shown in Fig. 3, with the maximum effect occurring during the linear phase. Therefore, any dose reduction during this period may eventually lead to a relapse. In fact, it has been shown in experimental systems that a dose reduction of 20% can result in a 50% reduction in cure rate even though the response rates may be maintained. The steeper the curve, the more likely it is that a dose reduction of the drug is going to impact its therapeutic efficacy. Therefore, empiric modifications of doses during anticancer treatment can substantially compromise outcomes.

The concept of dose intensity was introduced by Hryniuk and Goodyear [6, 7]. They defined the dose intensity of chemotherapy as the amount of drug delivered per unit of time expressed as milligram per square meter per week, irrespective of the schedule or route of administration. The dose intensity of each drug in the combination can thus be calculated. However, more important than the intended dose intensity, it is the received dose intensity that matters. There is a nice correlation between the received dose intensity in the clinical setting and the response rates of many tumors. The received dose intensity also reflects dose delays and dose reductions in the clinic and the feasibility of using the regimen in daily practice.

Summation dose intensity [8] refers to the sum of the dose intensities of the individual drugs in the chemotherapeutic combination and is useful in the design and interpretation of clinical trials.

There are three approaches to delivering chemotherapy in a dose-intensive manner

1. Dose escal3ation: The doses of the anticancer drug are increased keeping the interval between the doses the same.
2. Dose dense [9]: The interval between the doses is shortened, but the dose of the drugs is kept the same. The advantage of this approach is to prevent the regrowth of the tumor that occurs in between two doses, hence possibly avoiding the development of resistant clones emerging.
3. Sequential scheduling: Single agents are given in sequence and not in combination—therefore, the full dose intensity of each drug is maintained.

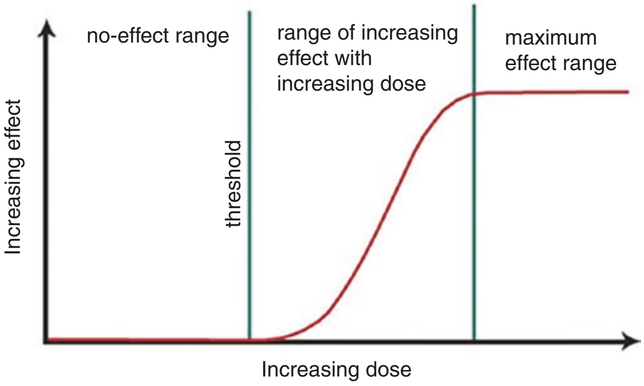

Fig. 3 The dose–response curve of a biological system

5.4 Cell Cycle and Chemotherapeutic Agents

Although the details of cell cycles are discussed elsewhere, it is worthwhile remembering a few salient aspects of their relationship with chemotherapeutic drugs. Most chemotherapeutic drugs act on tumor cells, which actively divide or undergo cell cycling. Drugs that act on specific phases of a cell cycle are called cell cycle phase-specific drugs. These act on tumors with a high growth fraction. Some drugs are however non-cell cycle-specific and these act on cells in both the resting (G0) and proliferating phases and are useful in treating tumors with a low growth fraction.

When the majority of cells in a tumor are in the G0 or resting phase, they are able to survive the toxic killing effects of chemotherapy and later regrow and produce tumor resistance.

6 The Principles of Hormonal Therapy for Cancer

Hormonal therapies that act through effects on steroid pathways and cancers that respond to this form of treatment are those arising in the organs that are heavily influenced by hormones, namely, breast cancer, prostate cancer, and endometrial cancer. Tumors arising from hormone tissues account for almost 35–40% [10] of all cancers, and these include breast and prostate cancers, which are the two most common cancers in women and men, respectively (Fig. 4).

Following Beatson's case reports on oophorectomy for breast cancer, there were several other case series and nonrandomized studies that took place in the adjuvant setting as well. In 1948, Paterson reported the first randomized trial of ovarian ablation in breast cancer at Christie Hospital, Manchester [11]. However, it was not until the early 1980s that the Oxford collaborative group was established, which brought together all the trials of chemotherapy and hormonal therapy for operable breast cancer [12].

In 1941, C. Huggins published pioneering work on the effect of castration, estrogen, and androgen injections on prostate cancer [13]. He won a Nobel Prize for his work in 1966.

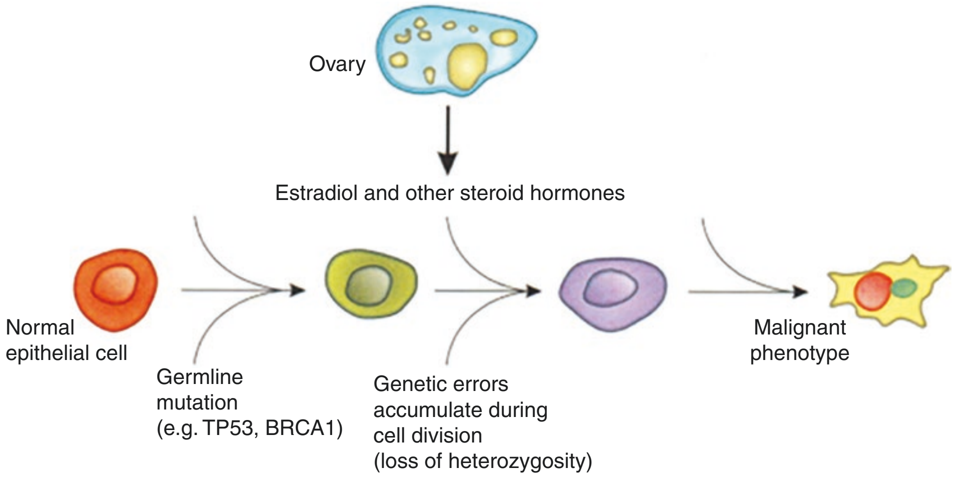
Ovary
Estradiol and other steroid hormones
Normal epithelial cell
Germline mutation (e.g. TP53, BRCA1)
Genetic errors accumulate during cell division (loss of heterozygosity)
Malignant phenotype

Fig. 4 The pathological basis for hormone-induced cancers

6.1 The Concept of Hormone Dependence

The carcinogenic effect of hormones has been demonstrated in both animals and humans. Hormones play a role in the origin and growth of tumors and cancers of the breast, uterus, prostate, anterior pituitary, adrenal cortex, ovary, and testis and can be induced by altering the endocrine milieu of the organ. In 1959, Furth et al. described the effect of hormones on various stages of development from normal cells to hyperplasia to a hormone-dependent tumor to an autonomous tumor still dependent on hormones and finally to a fully autonomous hormone-independent tumor [14]. This concept of hormone dependency is peculiar to certain cancers, and systemic hormonal therapies have been developed by taking advantage of this property.

There are two methods of destroying tumors by endocrine manipulation

1. Hormone deprivation
2. Hormone interference

It is important to understand the fundamental difference between a normal hormone-responsive target cell and its malignant hormone-dependent counterpart. For normal cells, hormones act as catalysts that help in growth and metabolism, but, when absent, the cell still survives. In contrast, malignant hormone-dependent cells are dependent for their survival on these hormones and often die when the source of hormones is removed. Hormone deprivation in breast or prostate cancers relies on this property to effectively kill these cancer cells.

Interestingly, supplying an excessive amount of hormones to the cancer cell can also kill it. This is known as hormone interference and is toxic to cancer cells leaving normal cells relatively unaffected. An example is breast cancer where the administration of excess estrogen can actually cause regression of the tumor. Not all hormone-dependent tumors respond to hormone interference, however.

Endocrine therapies are based on two principles

1. Ligand depletion—This can be achieved in three ways. By surgically removing the source of hormones, i.e., oophorectomy or orchiectomy, by blocking the trophic hormones in the pituitary gland using luteinizing hormone-releasing hormone (LHRH) analogues, or by inhibiting enzymes involved in steroid hormone synthesis.
2. Receptor blockade—This can be achieved using sex hormone receptor blockade like antihormonal agents.

6.2 The Effects of Hormonal Therapies on the Cell Cycle

As alluded to earlier, chemotherapeutic drugs have been described as either cell cycle phase-specific or cell cycle phase-nonspecific. Antiestrogens arrest the cell cycle in the G0/G1 phase, leading to growth inhibition of the tumor cell by decreased Rb phosphorylation [15]. This, in turn, results in fewer cells entering the S phase of the cell cycle. Further credence is given to this mechanism as the effect of antiestrogens can be reversed by the addition of estradiol, which rescues the tumor cell and allows it to enter the S phase within a few hours of its exposure. Antiestrogens inhibit the incorporation of thymidine into the DNA of estrogen receptor (ER)-positive breast cancer cells, thereby halting their growth and proliferation. Therefore, they are cytostatic rather than cytotoxic, causing tumor cell arrest in the early G1 phase and thereby decreasing the amount of cells synthesizing DNA in the S phase of the cell cycle [16].

Tumor cells that are in the actively dividing phase are thus sensitive to antiestrogens, but those that are in the plateau phase of the growth curve remain relatively resistant to these agents.

6.3 Breast Cancer and the Estrogen Receptor

When a breast cell undergoes a malignant transformation, it can retain all or some of its estrogen receptors or none at all. If the malignant cell expresses any amount of the target receptor, then its growth is still dependent on estrogen and these tumors respond to endocrine therapy. In case the receptors are lost during malignant transformation, the cell is independent of estrogen and these tumors fail to respond to endocrine treatment. Therefore, receptor assays must be part of the evaluation in all breast cancers. The development of antiestrogens was an important landmark in the therapy of breast cancer.

The principles underlying hormonal therapy of breast cancer include the following

- The tumor tissue must express hormone receptors for these drugs to be useful in breast cancer. No benefit is seen in tumors that do not express hormone receptors.
- Tumors that respond to previous hormonal therapy are likely to show responses to subsequent hormone treatments on progression.
- Fast-growing tumors with large-volume visceral involvement are less likely to respond to endocrine therapy.
- It is possible to get a “flare” reaction in the first few weeks of hormonal therapy with worsening of the symptoms such as bone pain. This is not an indication to discontinue treatment.
- Withdrawal responses may be observed in hormone-responsive tumors.
- It is possible to reverse endocrine resistance in the clinic by combining hormonal agents with targeted drugs.
- The combination of two hormonal agents has not been shown to be superior to using a single drug, except in the case of combining LHRH analogues with antiestrogens in premenopausal women.
- As long as the target receptor is expressed, endocrine therapy is useful in all clinical settings of breast cancer—neoadjuvant, adjuvant, and metastatic.
- Hormonal agents are not generally combined with chemotherapeutic agents as this combination may be detrimental.

6.4 Prostate Cancer and the Androgen Receptor

The androgen receptor is the target receptor for advanced prostate cancer, and both testosterone and dihydrotestosterone (DHT) bind to the receptor, leading to tumor growth. However, most antiandrogens are incomplete or partial androgen antagonists. Moreover, suppressing the testicular source of androgen does not work for long as androgens are also secreted by the adrenal glands, and, therefore, both these sources need to be blocked in order to inhibit tumor growth.

A major breakthrough in endocrine therapy was that LHRH released in a pulsatile manner controls the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary gland. If, on the other hand, LHRH is released in a continuous manner, then the pituitary gets desensitized and the secretion of LH and FSH decreases rapidly. The advent of LHRH agonist analogues has helped in achieving medical castration in men and oophorectomy in women.

It was also observed that patients with prostate cancer, who initially responded to antiandrogen treatment and subsequently progressed, then responded to the withdrawal of the antiandrogen. This is known as the antiandrogen withdrawal syndrome, which suggests that even after the antiandrogen therapies stop working the androgen receptor still plays a major role in the progression of tumor cells.

Most patients will progress within 18 months of antiandrogen therapy. These tumors still retain the androgen receptor, and, in some cases, it even tends to be overexpressed. Progression of the tumor despite antiandrogen therapy can be due to androgen receptor (AR) activation by other ligands, acquired hypersensitivity to androgen, or an activation of other autocrine pathways, such as fibroblast growth factor receptor (FGFR) or epidermal growth factor receptor (EGFR), etc.

The principles underlying hormonal therapy for prostate cancer include the following

- Unlike breast cancer, checking for the presence of the androgen receptor has no benefit in the use of hormonal therapy for prostate cancer as this receptor is expressed in the cytoplasm of prostate cancer cells.
- Blockage of testosterone is the basis of all treatments in advanced prostate cancer. Even if the tumor becomes hormone- and or castrate-resistant, androgen blockade has to be continued.
- In contrast to breast cancer, sequential responses to different hormonal therapies for prostate cancer are less common.
- Androgen blockade is useful in all clinical settings for prostate cancer—neoadjuvant, adjuvant, and metastatic.
- Responses to hormonal therapy are slow, generally taking 6–8 weeks.
- A flare reaction is commonly seen on initiation of antiandrogen therapy in the first few weeks of treatment. Special care should be taken in certain clinical situations like urinary obstruction or impending cord compression.
- Withdrawal responses are commonly seen but are rarely sustained.
- Despite the use of chemotherapy, androgen blockade cannot be discontinued.

6.5 Hormones and Other Tumors

Estrogen receptor (ER) and progesterone receptor (PR) expression is seen in a wide variety of solid tumors, including gynecological tumors. Progesterone agents have been useful in stabilizing disease in metastatic endometrial cancer, and patients with low-grade indolent disease are more likely to respond. A recent meta-analysis of 39 studies has shown a duration of response of about 3 months with a median survival of about 10.8 months. Response rates ranged from 26% in ER-positive patients and 35% in patients expressing PR [17]. Tamoxifen, however, has not proven useful. The use of hormonal agents in ovarian cancers has been disappointing.

Although ERs have also been detected in hepatocellular carcinoma, lung cancer, meningiomas, renal cell carcinomas, and sarcomas, there is little evidence for endocrine therapy use in these indications.

7 The Principles of Targeted Therapy for Cancer

This section deals with targeted therapy for cancer, which has gained momentum in the last 15 years. Chemotherapy for cancer depends on drugs that lack selectivity for tumor cells and primarily consists of cytotoxic agents that have a narrow therapeutic index as described earlier. Recent efforts have focused on exploiting biological processes or targets specific for tumor cell growth. Although these drugs have proven useful for both hematological [chronic myelogenous leukemia (CML)] malignancies and solid tumors, they are not without toxicity to normal tissues, albeit different to those caused by chemotherapy.

Targeted therapies have demonstrated their usefulness in both adjuvant and metastatic settings. An increased knowledge of cancer biology has led to identifying various proteins and pathways essential to the survival of cancer cells. Targeting these proteins and pathways is the mainstay of targeted molecular therapy [18–20]. Table 3 shows the types of molecular targeted agents that have been developed.

7.1 Druggability of Molecular Targets

The most important step in developing a successful targeted treatment is validation of the target in experimental systems. Thereafter, the "druggability" of the target needs to be determined. Targeting a single protein may be limiting in its efficacy unless there is "oncogene addiction" [21]. This refers to the complete dependence of the tumor cell on a particular protein for its survival and proliferation. The inhibition of the BCR-ABL protein by imatinib in chronic myeloid leukemia is an exemplary example of oncogene addiction, and, since its development, there have been few similarly effective drugs for other indications. Oncogene addiction also explains why the tumor continues to benefit from sustained inhibition of the pathway that it is dependent on, despite clinical progression (e.g., trastuzumab can be used beyond progression in human epidermal growth factor receptor 2 (Her2)-positive metastatic disease).

Table 3 Types of molecularly targeted compounds that have been developed

Agent	Potential target(s)	Comments
Antisense oligonucleotides	RNA, DNA and proteins	Not fulfilled their promise as therapeutic agents
SiRNA	RNA	In early clinical trials
Gene therapy	Neoplastic cells, immune mediator cells	Oncolytic viruses have been used in the treatment of malignant gliomas
Ribozymes and DNAzymes	RNA and DNA in tumour cells	Angiozyme most widely studied. Trials ongoing
mABs	Growth factors, growth factor receptors, cell surface antigens	Examples are trastuzumab for breast cancer, cetuximab for colorectal cancer
Modified peptides or biologic response modifiers	Circulating proteins, cell surface antigens, intra and extracellular proteins	Somatostatin analogues denileukin diftitox used to treat CD25 expressing recurrent CTCL
Small molecules	All of the above targets	Includes kinase inhibitors, proteosome inhibitors, matrix metalloprotease inhibitors, heat shock protein inhibitors and inhibitors targeting apoptosis

Therefore, choosing a targeted therapy is vitally important. Even if it is cytostatic in nature, it must be capable of causing either differentiation or prolonged growth suppression of tumor cells either as a single agent or as part of combination therapies. Developing rational combinations of targeted agents may also be more effective.

Simply put, cancer results as a consequence of oncogene protein activation or loss of tumor suppressor proteins. It is much easier to develop inhibitors of activated proteins than to replace suppressor proteins that have been lost (e.g., restoring the function of p53 or retinoblastoma proteins poses a significant technical challenge) [22]. However, other methods of using the phenomenon of loss of tumor suppressors have been developed. One such group of drugs are poly (ADP-ribose) polymerase (PARP) inhibitors, which produce synthetic lethality in breast cancer gene (BRCA)-mutated tumors [23].

At present, the proteins amenable to successful targeting are those activated by mutations, e.g., BCR-ABL, Eml-Alk4, EGFR, or those that are overexpressed or amplified, e.g., Her2, and are critical for the survival of malignant cells. The kinases are especially important in the pathways of cell growth, metabolism, migration, proliferation, and survival. Phosphorylation is a central process for pathway activation. Both kinases and phosphatases remove and add phosphate molecules, respectively, to the key functional proteins in these pathways [24]. Kinases therefore act as signal transducers and, when mutated, become attractive targets for inhibition of the tumor cell.

Usefulness of a targeted treatment depends on a number of factors

- Adequate delivery of the agent to the tumor cell
- Adequate binding of the agent to the tumor cell
- The presence of the agent within the tumor cell for sufficient time to produce a meaningful effect
- Unanticipated toxicities of the agent on the normal tissue—both acute and chronic
- Disadvantages of antibodies include large size and complex structure, making absorption difficult and the presence of alternate binding proteins in the blood and normal tissue, which may reduce the efficacy.

Validation of a target includes a number of important considerations

1. The particular gene and its target protein should be selectively expressed on the tumor tissue as compared to the normal tissue.
2. The protein should be essential for the survival, proliferation, and malignant behavior of the tumor cell.
3. Inhibition of the protein should lead to growth arrest or death of the malignant cell and produce the desired clinical effect.
4. The protein should not be expressed in the key normal tissues such as bone marrow progenitors, intestinal epithelium, heart, kidneys, and brain; otherwise, there would be significant toxicity.
5. The importance of the protein to be targeted in the functioning of normal cells should be elucidated before attempting clinical trials.
6. Most importantly, the availability of appropriate biomarkers for the targeted therapy is critical to identify responders that can further help in developing the drug in clinical trials.
7. Biomarkers can also help in optimizing the dose and schedule and also serve as surrogates for response (e.g., Her2 positivity in breast cancer treated with trastuzumab).

Table 4 Features shared by most small-molecule receptor tyrosine kinase inhibitors

Binding to the ATP site which may be an active or inactive conformation or even both
Usually inhibit more than one kinase but degree of selectivity varies
Oral treatments where half lives allow daily or twice daily dosing
Acceptable toxicities at clinically effective doses (Good Therapeutic Index)
Most are cytochrome P450 substrates therefore drug interactions and pharmacogenomics is important
Major side effects seen are due to the predominant protein inhibited EG skin toxicity with EGFR inhibitors

Perhaps the most attractive and well-studied targets are the growth factor receptors, many of which are receptor tyrosine kinases. These receptors are often overexpressed in malignant cells. In others, they appear to be mutationally activated. Their presence on the cell surface also makes them easily accessible for inhibition by antibodies and by small-molecule kinase inhibitors. Growth factors normally bind to these receptors on tumor cells and promote the tumor's metastatic potential. Receptor tyrosine kinase inhibitors share a number of features, which are listed in Table 4.

Signals from growth factor receptors travel downstream though multiple switches, activating a host of pathways, which ultimately reach cytoplasmic and nuclear effectors. The Ras and the phosphoinositide 3-kinase (PI3K) pathways are among the most extensively evaluated, and a host of actual and potential targets have been developed and identified, respectively. Figure 5 shows both these pathways.

Molecular targeted therapy is now part of standard anticancer treatment. Most of these inhibit the target directly, although the newer antibody drug conjugates (ADCs) deliver the cytotoxic drug directly into the tumor cell. Monoclonal antibodies have been approved for solid tumors such as breast, colorectal, lung, head and neck cancers, renal cell carcinoma, ovarian cancer and glioblastoma, and hematological malignancies like acute myeloid leukemia (AML), B-cell chronic lymphocytic leukemia (B-CLL), non-Hodgkin's lymphoma, and others. Receptor tyrosine kinase inhibitors are available for a number of targets, including BCR-ABL, C-KIT, platelet-derived growth factor receptor (PDGFR), EGFR, Her2, and vascular endothelial growth factor receptor (VEGFR).

This is an exciting period for targeted therapies, and the list of agents is likely to grow exponentially over the next decade. An improved understanding of the mechanisms of resistance of these agents and the development of combinations of targeted drugs are likely to increase the efficacy of these agents in the clinic.

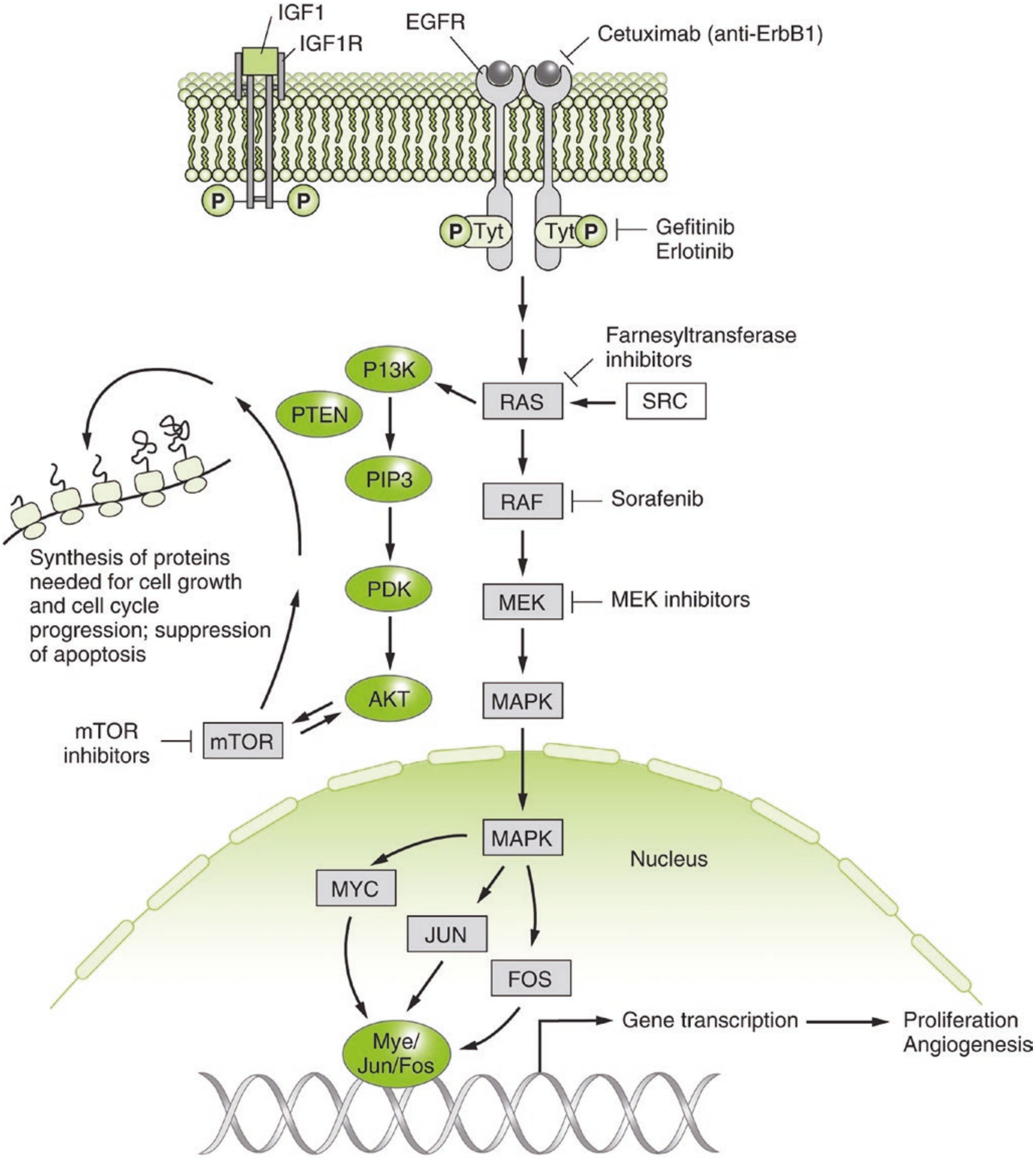
IGF1
IGF1R
EGFR
Cetuximab (anti-ErbB1)
P
P
P
Tyt
Tyt
P
Gefitinib
Erlotinib
Farnesyltransferase
inhibitors
P13K
PTEN
RAS
SRC
PIP3
RAF
Sorafenib
Synthesis of proteins
needed for cell growth
and cell cycle
progression; suppression
of apoptosis
PDK
MEK
MEK inhibitors
AKT
MAPK
mTOR
inhibitors
mTOR
MAPK
Nucleus
MYC
JUN
FOS
Mye/
Jun/Fos
Gene transcription
Proliferation
Angiogenesis

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Fig. 5 Two signaling pathways stimulated by insulin-like growth factor-1 (IGF-1) and epidermal growth factor (EGF) ligands, which activate downstream signals through the PI3K and RAS pathways

8 The Principles of Cancer Immunotherapy

Cancer immunotherapy has developed very rapidly since 2010, although its development has a long history. In fact, the Nobel Prize for medicine in 2018 was jointly awarded to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation" [25, 26]. The goal of this treatment is to kill cancer cells by reactivating the immune system.

8.1 The Immune System

Our immune system is a complex one with both innate and adaptive systems. The innate system involves neutrophils and natural killer cells, whereas the adaptive system contains B cells, which produce antibodies and lymphocytes that consist of CD4 helper cells, CD8 killer cells, and forkhead box P3+ (FOXP3+) regulatory T cells. This adaptive system, which fights viral infections, also has the ability to control and eliminate cancer cells. Adaptive immune cells recognize foreign cells in the body by antigen presentation.

8.2 Antigen Presentation and Recognition

T-cell receptors found on the surface of B or T lymphocytes recognize the cancer cell, when the major histocompatibility complex (MHC) presents a small peptide fragment of the cancer protein to the lymphocytes. This is called antigen presentation. The final outcome of antigen presentation and recognition depends on the balance achieved by the costimulatory molecules or immune checkpoints on the target cancer cell and the lymphocyte. This is a highly delicate balance, and, if the signals are positive, then the immune cells get primed to attack the antigen or, in this case, the cancer cell. If, on the other hand, they are negative, then the antigen is accepted as normal and the immune system is inactivated. The immune checkpoints, which are relevant to cancer, include CTLA4, PD1 PD-L1.

8.3 Immunoevasion

The fact that a cancer becomes clinically detectable implies that it has evaded the immune system. This is known as immunoevasion [27]. During the growth of a tumor, cancer cells produce several aberrant proteins called "neoantigens," which can be recognized, as mentioned earlier, by antigen presentation. Our immune system therefore has many opportunities to eliminate the tumor, and this is referred to as immunosurveillance [28]. In other cases, the cancer cells and the immune system reach some sort of equilibrium and coexist. If for any reason, this balance gets disturbed and there is immunosuppression due to old age or other illnesses, then cancer cells escape the immune system and start to grow.

Immunotherapy for cancer aims at restoring immunosurveillance and getting rid of the cancer cells.

8.4 Cancer Immunotherapy

Cancer immunotherapy can be categorized as follows

- It can be active where it actively stimulates the immune system or passive where it simply alters immune signaling.
- The treatment can be specific, acting against a known target or antigen, or nonspecific, where the immune system is stimulated in general.

Figure 6 shows the types of immunotherapies available today. Some of these are discussed below:

Chimeric antigen receptor T (CAR-T) cells are a form of active nonspecific type of cancer immunotherapy that is increasingly being used and studied today. These T cells are derived from the patient (autologous) and genetically modified in vitro to express cancer recognition molecules on their surface. It is also referred to as adoptive cell therapy. Currently, CAR-T cells have been approved in the setting of relapsed adult NHL and childhood B-cell acute lymphocytic leukemia (B-ALL). Trials in the first-line setting are ongoing and in several other indications such as myeloma, AML, and even in some solid tumors like breast cancer. The major side effects are cytokine release syndrome and cytokine-related encephalopathy syndrome.

Humanized monoclonal antibodies have been available for over two decades now and are a prime example of passive specific immunotherapy. They cause death of cancer cells by direct actions, complement-dependent cytotoxicity (CDCC), and antigen-dependent cellular cytotoxicity (ADCC). Rituximab for lymphomas and trastuzumab for breast cancer are perhaps the most familiar and the most used antibodies in cancer treatment.

Immune checkpoint inhibitors are also a type of passive specific immunotherapy. Immune checkpoints play a key role in immunoevasion as discussed earlier, and inhibition of these checkpoints can restore immunosurveillance, thereby eliminating the cancer cells. These molecules are increasingly being used in the clinic, either alone or in combination with chemotherapy, and have been approved for over 10 solid tumors. Many more are in clinical trials.

The focus has been on the negative regulatory molecules in order to control immune checkpoint signaling. The mechanism of action of immune checkpoint inhibitors is relatively

	Non-specific	specific
Active	Bacillus Calmette-Guerin (BCG) Cytokines Oncolytic viruses	Cancer vaccines Oncogenic virus vaccines CAR-T-cells
Passive	Lymphokine-activated killer cells Tumour-infiltrating lymphocytes (TILS)	Monoclonal antibodies Radioimmunotherapy Ex vivo expanded antigen-specific T-cells Immune checkpoint inhibitors

Fig. 6 Types of immunotherapies available. [Adapted from Davis et al. [29]]

straightforward. As long as the immune system is in balance, there is no change. In case the tumor cell increases checkpoint signaling by increasing CTLA4 and PDL1, then the immune system gets inhibited. This is often the situation in metastatic tumors. By blocking the antibodies (CTLA4 and PD1/PD-L1) that block this signaling, this balance can be restored and the immune system can regain control of the cancer.

Important considerations when using immune checkpoint inhibitors to treat patients are as follows

- Checkpoint inhibitors only help some patients—only a minority of patients reap dramatic and enduring benefits from this treatment, and this is important for both the clinician and patient to keep in mind during treatment.
- Benefits from checkpoint inhibitors take long to occur—sometimes many months. Similarly, the side effects are also long drawn out. In fact, some patients experience a pseudoprogression after 6–8 weeks of treatment, and, if the patient is clinically well with imaging indicating progression, it is worthwhile to wait a further 8 weeks and continue treatment before prematurely stopping it.
- Disease stabilization is more common than actual shrinkage of the tumor, and this is indeed a reasonable end point while treating metastatic disease. Patients can live with disease stabilization for longer and with a good quality of life.
- Many cancers do not respond to checkpoint inhibitors for reasons that are not clear.

  Melanomas, lung cancers, renal and bladder cancers seem to respond to this treatment. However, prostate cancer and most breast cancers, ovarian cancers, and colorectal tumors do not respond.
- The side effects of checkpoint inhibitors result from immune overactivation. The common side effects are gastrointestinal, dermatological, and endocrine. In fact, any illness in a patient being treated with immune checkpoint inhibitors should be considered as autoimmune unless proved otherwise. They are slow in onset and slow to recover. Treatment consists of supportive care and immunosuppression.
- Patients on checkpoint inhibitors must continue to receive good palliative care as responses are rare and patients will continue to progress and die from the disease.

To summarize, we have looked at different systemic therapies for cancer and the principles that govern their use. The treatment of cancer is continuously evolving. Now, we have not only chemotherapy and hormonal treatments in our armamentarium but also a host of targeted therapies and immunotherapies. It is likely that a combination of two or more types of systemic therapies will prove more successful than using them alone. Further research and study are warranted to develop new and effective combinations for our patients in the clinic.

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Pediatric Oncology

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Abbreviations

AAR	Age-adjusted rate
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
CNS	Central nervous system
GBD	Global Burden of Disease
HIC	High-income country
IARC	International Agency for Research on Cancer
IAP	Indian Academy of Pediatrics
ICMR	Indian Council of Medical Research
IICC-3	International Incidence of Childhood Cancer
LMICs	Low- and middle-income countries
NCI	National Cancer Institute
NCRP	National Cancer Registry Program
NHL	Non-Hodgkin's lymphoma
NTP-PPO	National Training Program in Practical Pediatric Oncology
PBCRs	Population-based cancer registries
PHO	Pediatric Hematology Oncology
SEER	Surveillance, Epidemiology, and End Results
SNS	Sympathetic nervous system

1 Introduction

Childhood cancers are extremely rare compared to those of the adult population, with approximately 300,000 children diagnosed worldwide with cancers annually in the 0–19-year age group [1, 2]. These represent less than 1% of all cancers in developed countries, but, in developing countries with a higher proportion of children, the incidence can be five times higher [2]. The incidence of cancer rates in children is steadily increasing over the years, with reported rates in 0–14-year-olds showing a jump from 124 per million person years in the 1980s to 140.6 per million person years in 2001–2010 [1]. With increasing implementation of programs aimed at detection, treatment, and surveillance of infectious and many non-infectious diseases, cancer has emerged as one of the leading causes of death in children and adolescents around the world with an estimated 80,000 cancer-related deaths in children per year worldwide. The disparities evident in the incidence and patterns of childhood cancers across high-income countries (HICs) and low- and middle-income countries (LMICs) extend to cure rates as well, with 80% of children with cancer cured of disease in HICs compared to 20% in LMICs [3]. The stark inequalities seen in both survival and mortality across these countries are palpable in the financial allocation for cancer care also, with only 5% of the global resources for cancer care invested in LMICs [4]. The trends in incidence, mortality, and patterns of childhood cancers are mostly obtained from cancer registries, which are an indispensable source of information to inform policies addressing childhood cancer control and also to assess the impact of such efforts.

Pediatric cancers differ from those in adults on various fronts ranging from biology, patterns of spread, histology, response to treatment, late effects, and cure rate. Unlike adult cancers, most pediatric cancers are not caused by modifiable risk factors. Moreover, children have less comorbidities compared to adults, but the developing organ systems, which are immaturely functional at earlier ages, present a distinct set of complications related to treatment, both acute and chronic. The increased responsiveness of most childhood cancers to therapy, which stems from the fact that the majority of pediatric cancers are "embryonal" in nature, translates to improved cure rates with timely diagnosis and treatment compared to adult cancers. Nevertheless, treatment of pediatric cancers warrants specialized diagnostic and treatment facilities, which can handle the specific complications anticipated in children. This chapter will provide a general overview of pediatric cancers and the epidemiology and

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challenges in the management of pediatric cancers in resource-constrained areas.

2 Epidemiology of Childhood Cancers in the World

With nearly 90% of the world's children residing in LMICs, they constitute the major proportion of childhood cancers, nearly 84% [5]. However, global estimates regarding the incidence of cancers demonstrate a striking gap in the data available from HICs and LMICs, as evident from following registry-based analyses, which reveal that only 5–12% of LMICs are covered in these datasets: International Incidence of Childhood Cancer (IICC-3) [1], CONCORD-3 [6], GLOBOCAN 2012 [7], and Global Burden of Disease (GBD) 2016 studies [8]. The above studies represent the four most comprehensive sources for estimates of childhood cancer incidence, survival, and mortality from data published between 2000 and 2018. In addition to this, estimates of cancer incidence and survival based on population-based data from the United States are available from the Surveillance, Epidemiology, and End Results (SEER) program coordinated by the National Cancer Institute (NCI) [9]. These global, regional, and national estimates of the incidence, patterns, survival, and mortality are essential inputs to inform health policy decisions to design, implement, expand, strengthen, and disseminate various health-care services and evaluate the impact of the above decisions. Their role in etiological research and in improving outcomes cannot be understated.

2.1 Published Estimates of Global Cancer Burden

The published estimates of cancer incidence, survival, prevalence, and mortality based on four major research programs are summarized in the following Table 1 [10].

The global estimates of new cases and cancer deaths in children (0–14 years) in 2012 as per GLOBOCAN 2012 and GBD 2016 are presented in Table 2 [10].

The International Agency for Research on Cancer (IARC) has made estimates of childhood cancer incidence by world region and cancer type for the year 2018 for Lancet

Table 1 A summary of the four major published studies estimating childhood cancer incidence, survival, prevalence, and mortality [9]

	IICC-3	GLOBOCAN 2012	GBD 2016	CONCORD-3
Publication year	2017	2015	2017	2018
Years included	2001–2010	2012	1990–2015	2000–2014
Data sources	Population-based registries	Cancer incidence in five continents, individual population-based registries, WHO vital statistics, survival data	Cancer incidence in five continents, individual population-based registries, vital statistics (WHO and national), verbal autopsies	Population-based registries
Global estimates	Not applicable	Yes	Yes	Not applicable
Number of registries	153	375	562	322
Proportion of LMIC registries	11%	7%	12%	5%
Countries included	62	184	195	71
Age strata (years)	0–4, 5–9, 10–14, 15–19	0–14	0–4, 5–9, 10–14, 15–19	0–14
Outcomes estimated	Incidence	Incidence, mortality	Incidence, prevalence, mortality, disability-adjusted life years (DALYs)	5-Year net survival
Cancers included	Leukemias, lymphomas, CNS tumors, neuroblastoma, kidney, hepatic, bone, soft tissue sarcoma, germ cell tumors, epithelial tumors, others and unspecified	Leukemias, Hodgkin's lymphoma, NHL, CNS, kidney, liver, Kaposi sarcoma	ALL, AML, Hodgkin's lymphoma, NHL, CNS, kidney, liver	ALL, lymphomas, CNS tumors
Uncategorized cancers	0%	30%	29%	Not applicable
Global number of incident cases in the 0–19-year annual estimate	Not applicable	163,284	240,942	Not applicable
Global number of cancer deaths in the 0–19-year annual estimate	Not applicable	79,956	90,075	Not applicable

Table 2 Global estimates of new cancer cases and cancer deaths [9]

	Number of cases		Number of deaths	
	GLOBOCAN 2012	GBD 2016 [uncertainty interval (UI)]	GLOBOCAN 2012	GBD 2016 (UI)
Leukemias	49,752	63,230 (57,517–67,989)	27,775	29,165 (26,846–32,673)
Acute lymphoblastic leukemia	Not estimated	30,089 (28,217–33,082)	Not estimated	12,489 (11,429–14,828)
Acute myeloid leukemia	Not estimated	11,631 (10,376–13,178)	Not estimated	5811 (5030–6840)
Brain and nervous system tumors	20,105	29,967 (27,612–32,022)	10,458	15,828 (14,066–17,532)
Neuroblastoma	Not estimated	Not estimated	Not estimated	Not estimated
Non-Hodgkin's lymphoma	16,514	17,350 (14,722–18,746)	7223	10,974 (9195–12,375)
Kidney tumors	9656	13,794 (12,988–14,437)	5547	2481 (2305–2654)
Bone tumors	Not estimated	Not estimated	Not estimated	Not estimated
Hodgkin's lymphoma	6774	5220 (4270–5946)	1737	2421 (1798–3069)
Rhabdomyosarcoma	Not estimated	Not estimated	Not estimated	Not estimated
Retinoblastoma	Not estimated	Not estimated	Not estimated	Not estimated
Categorized cancers	114,202	133,672 (119,243–146,284)	57,861	62,503 (54,630–71,192)
All cancers in 0–14 years	163,284	184,856 (171,441–191,140)	79,956	82,552 (77,182–88,092)
Uncategorized cancers (other neoplasms)	49,082	51,184	22,095	20,048
Proportion uncategorized	0.3	0.28	0.28	0.24

Table 3 Estimated age-standardized incidence rates for children with cancer for 2018, by world region [10]

World region	Age-standardized incidence rate (per million person years)	95% Uncertainty interval	Number of children
Africa, north	105.4	83.2–127.6	7587
Africa, sub-Saharan	59.5	54.9–64.1	24,584
America, Caribbean	148.7	133.1–164.3	8780
America, south	135.7	128.8–142.6	13,500
America, north	167.8	162.9–172.6	10,781
Asia, eastern	163.2	156.9–169.4	43,144
Asia, south-central	79.9	70.7–89.1	44,098
Asia, southeastern	122.9	108.5–137.4	20,280
Asia, western	146.5	134.4–158.6	11,162
Europe, eastern	159.1	150.0–168.2	7305
Europe, northern	150.6	142.0–159.2	2658
Europe, southern	175.1	163.6–186.5	3791
Europe, western	169.2	162.0–176.4	4852
Oceania	152.0	137.2–166.8	1362

Table 4 Estimated age-standardized incidence rates for children with cancer for 2018, by cancer type [10]

Cancer type	Age-standardized incidence rate (per million person years)	95% Uncertainty interval	Number of children
Leukemia	49.1	47.9–50.4	91,463
Lymphoma	15.5	14.7–16.3	30,410
CNS tumors	30.4	29.4–31.4	57,457
Sympathetic nervous system tumors	10.9	10.3–11.5	19,235
Retinoblastoma	4.7	4.2–5.1	8132
Renal tumors	8.3	7.8–8.8	14,871
Hepatic tumors	2.6	2.2–2.9	4578
Bone tumors	5.7	5.3–6.1	11,597
Soft tissue sarcoma	9.1	8.7–9.5	17,327
Germ cell and gonadal tumors	5.3	5.0–5.7	10,230
Epithelial tumors and melanoma	5.1	4.7–5.5	10,332
Others and unspecified	1.1	0.9–1.2	1977

Commission, which are detailed in Tables 3 and 4, respectively [11].

These published studies have minimal data from LMICs with severe underestimation of the actual global burden of childhood cancers. It is estimated that 44% of all children with cancer globally remain undiagnosed and underreported due to barriers in access to health care with >50% underreporting in LMICs [11]. Underdiagnosis (due to poor access to diagnostics and health care), underregistration (due to underdiagnosis, inadequate capacity resources, and underreporting), poor quality of the registered data, different formats and coding systems, passive follow-up of registered patients for survival data (especially when registries are linked only to official public record systems like the death registration system, social and health insurance, electoral registers, or hospital records, which are inefficient or difficult to access), underregistration of privately treated patients, and noninclusion of all childhood tumors, especially solid tumors, are among the reasons for this underestimation of various indices.

2.2 Surveillance, Epidemiology, and End Results (SEER) Data

Approximately 16,400 children and adolescents <20 years of age are diagnosed annually in the United States corresponding to an age-adjusted incidence rate for all cancers of 15.8 cases per 100,000 person years for children (0–14 years) and 21.7 per 100,000 person years for adolescents (15–19 years) with 1300 and 600 cancer-related deaths in 2010 in the <15 year and 15–19 year cohorts, respectively.

In children aged 0–14 years, acute lymphoblastic leukemia (ALL) was the most common cancer (25.4%), followed by tumors of the central nervous system (CNS), primarily brain tumors (20.6%). The most common non-CNS solid tumor was neuroblastoma (7.0%), followed by Wilms tumor (5.4%). The remaining were non-Hodgkin's lymphoma (NHL) (5.9%), acute myeloid leukemia (AML) (5.0%), and other cancers like Hodgkin's lymphoma, rhabdomyosarcoma, nonrhabdomyosarcoma soft tissue sarcomas, germ cell tumors, retinoblastoma, and osteosarcoma constituting 2–4% each. In the 15–19-year-old group, Hodgkin's lymphoma (16.0%) and germ cell tumors (13.7%) were the most common followed by CNS tumors (9.7%). Non-Hodgkin's lymphoma (8.0%), melanoma (7.0%), thyroid cancer (8.7%), nonrhabdomyosarcoma soft tissue sarcoma (6.0%), osteosarcoma (4.1%), and Ewing sarcoma (2.0%) were seen in a higher proportion, whereas certain other cancers like rhabdomyosarcoma (1.7%), neuroblastoma (0.3%), and Wilms tumor (0.2%) are seen at extremely low rates compared to the 0–14-year-old age group [9].

Male preponderance for ALL, Hodgkin's lymphoma, NHL, retinoblastoma, hepatoblastoma, Ewing sarcoma, rhabdomyosarcoma, and nasopharyngeal carcinoma were seen in the 0–14-year age group with female preponderance observed for thyroid cancer in this age group. There were a few differences from the above noted in the 15–19-year-old age group with equal distribution of Hodgkin's lymphoma in both sexes, male predominance in germ cell tumors and osteosarcoma, and female predominance in Wilms tumor and melanoma.

2.3 Estimates of Global Childhood Cancer Survival

CONCORD-3 covered the 5-year net survival (the cumulative probability of surviving up to 5 years after diagnosis, after correcting for other causes of death) for acute lymphocytic leukemia, lymphoma, and CNS tumors during the period 2000–2014 for the 0–14 year age group but had only 5% representation from LMICs. The 5-year net survival for the United States based on this for various diseases were as follows: acute lymphoblastic leukemia and lymphoma- 89.6% [95% confidence interval (95% CI): 88.8–90.3%], acute myeloid leukemia- 67% (95% CI: 64.4–69.6%), Hodgkin's lymphoma- 100%, non-Hodgkin's lymphoma- 90.4% (95% CI: 88.6–92.2%), ependymoma and choroid plexus tumors- 84.2% (95% CI: 81.2–87.2%), astrocytoma-82.7% (95% CI: 81.3–84%), embryonal brain tumors- 69.4% (95% CI: 66.4–72.4%), other gliomas- 58.2% (95% CI: 55.4–60.9%).

A survival module to model the 5-year net survival for childhood cancers for 200 countries worldwide was developed to provide a comprehensive estimate of global childhood cancer survival, which was lacking for many LMICs [11, 12]. In 2015–2019, the global 5-year net survival was 37.4% [95% uncertainty interval (95% UI): 34.7–39.8%], ranging from 11.6% (95% UI: 8.7–14.8%) in Africa to 39.6% (95% UI: 35.1–43.6%) in Asia, 55% (95% UI: 51.2–58.7%) in Latin America and the Caribbean, 64.4% (95% UI: 58.9–69.2%) in Oceania, 74.3% (95% UI: 71.9–76.4%) in Europe, and 83.0% (95% UI: 81.6–84.4%) in North America. The modeled estimate of the 5-year net survival was only 7.4% (95% UI: 5–10.7%) in low-income countries but 79.8% (95% UI: 8.7–80.8%) in high-income countries, highlighting the striking gap across these countries.

3 Epidemiology of Childhood Cancers in India

3.1 Estimates of Incidence and Patterns

In India, cancer is the ninth commonest cause for death in children aged 5–14 years compared to developed nations where cancer is the leading cause of disease-related death in this age group [5, 13]. Merely 2% of all deaths in the pediatric age group are due to cancer in India compared to England and Wales where cancer contributes 20% to disease-related death in children, second only to accidents and injuries (21%) [14]. The National Cancer Registry Program (NCRP), run by the Indian Council of Medical Research (ICMR) covering population-based cancer registries (PBCRs), is the source of incidence and patterns of childhood cancers in India. The latest report (2016) covers <10% of country's population and provides data from 30 PBCRs, though with disparities in rural and regional representation [13]. This report shows a rise in childhood cancer incidence from 38–124 per million (pm) children in 2001–2004 and 11.3–159.6 pm in 2009–2011 to 6–860 pm in 2011–2014. Interestingly, childhood cancers showed a marginal reduction relative to cancers in all age groups in the same time periods (3.2% in 2001–2004, 3.1% in 2009–2014, and 2.5% in 2011–2014). The regional estimates of childhood cancer incidence in India are provided in Table 5.

In the NCRP report, males had a higher incidence (4–551 pm) compared to females (2–309 pm) with a male-to-female ratio of 1.6:1, slightly higher than that in the developed world with a ratio of 1.2:1 [2]. The highest incidence of childhood cancers overall and in males separately was seen in the 0–4-year age group, whereas females had the highest incidence in the 10–14-year age group. The relative proportion of childhood cancers in boys was the lowest in the Nagaland PBCR (northeast region) (0.7%) and the highest in the Delhi PBCR (north region) (5.4%), and, in girls, it varied from 0.5% in the East Khasi Hill district PBCR (northeast region) to 3.5% in the Naharlagun excluding Papum Pare PBCR (northeast region). The predominant childhood cancer was leukemia, with 70% being lymphoid leukemia. The second most common was lymphomas followed by CNS tumors, a reversal of what is seen in the developed world. Among lymphomas, NHL was slightly (54%) higher than Hodgkin's lymphoma, similar to the developed world, though an earlier review showed the reverse [15]. Leukemias, lymphomas, and CNS tumors had the highest incidence among the 0–4 year, 10–14 year, and 5–9 year age groups, respectively. Genitourinary, eye, and liver tumors were the highest among the 0–4-year age group and bone tumors among the 10–14 year age groups. The incidence of common cancer types in children is detailed in Table 6.

Table 5 Childhood cancer incidence in India as per location of the registry [13]

Registry location	Cancer incidence AAR per million (% of childhood cancers out of all cancers)		
	Boys	Girls	Total
National data	4–551 (0.7–5.4)	2–309 (0.5–3.5)	6–860 (0.7–4.4)
North	69–551 (2.4–5.4)	41–309 (1.3–3.2)	110–860 (1.8–4.4)
South	102–158 (1.8–2.9)	82–108 (1.3–1.5)	184–240 (1.5–2.4)
East	30 (1.1)	29 (1.1)	59 (1.1)
West	12–156 (2–4.5)	12–89 (0.9–2.5)	24–245 (1.5–3.4)
Central	44–65 (2.6–2.9)	26–47 (1.5–1.9)	70–112 (2.4–2.6)
Northeast	4–71 (0.7–3.3)	2–51 (0.5–3.5)	6–116 (0.7–2.7)

Age-adjusted rates (AARs) for 11 selected broad types of childhood cancers [leukemias, lymphomas, central nervous system (CNS) tumors, sympathetic nervous system (SNS) tumors, retinoblastoma, renal tumors, hepatic tumors, bone tumors, soft tissue sarcomas, germ cell tumors, and others]

3.2 Estimates of Cancer-related Mortality and Survival in India

PBCR survival data for childhood cancers have been reported from Bangalore and Chennai where the 5-year overall survival for all childhood cancers combined is 37–40% [15]. Hodgkin's lymphoma and Wilms tumor had the highest survival with approximately two-thirds of the children surviving for 5 years or more. The survival for retinoblastoma and germ cell tumors was less than that of the developed world. The prognoses for CNS tumors and leukemias were also low, with the 5-year survival rates being 25% and 33%, respectively. A higher survival rate is seen in those treated at specialized cancer treatment centers. In India, the mortality rate (adjusted to world standard population) varies from 14 to 34

Table 6 Incidence of common types of cancers in children in India in AAR per million children [13]

Diseases	Age group (years)						Total incidence
	0–4		5–9		10–14		
	Male	Female	Male	Female	Male	Female	
Leukemia	33.0	17.9	28.5	15.3	23.3	13.3	131.3
Lymphoid	25.7	13.0	19.6	11.0	15.9	6.9	92.1
Myeloid	5.1	3.2	6.7	3.2	5.0	5.3	28.5
Unspecified	22.2	1.7	2.2	1.1	2.4	1.1	10.7
Lymphoma	2.8	1.9	10.8	3.4	13.0	4.9	37.8
Non-Hodgkin's lymphoma	2.3	1.4	4.8	2.1	7.2	2.7	20.5
Hodgkin's lymphoma	2.5	0.5	6.0	1.3	5.8	2.2	17.3
CNS tumors	5.5	4.4	8.7	6.5	7.9	4.7	37.7
Genitourinary tumors	8.	5.1	2.0	2.5	1.6	5.2	24.8
Bone tumors	2.6	1.7	3.5	2.7	7.7	6.2	24.4
Eye tumors	7.7	5.1	1.8	0.5	0.1	0.3	15.5
Gastrointestinal tumors	0.5	1.0	1.6	0.8	1.8	1.0	6.7
Liver tumors	2.9	1.5	0.6	0.3	0.3	0.1	5.7

per million children per year, but, when the incidence of cancer is factored into this calculation (as incidence rates are low in some parts of the country), values depicted as the mortality incidence (M:I) ratio rather than mortality rates provide more clarity. The M:I ratio varies from 17 to 72% in India as compared to 20 to 24% in the United States and Britain [2]. The largest contributor to mortality in Britain is CNS tumors, but, in India, leukemia is the major contributor to cancer-related mortality.

In a study designed to procure direct estimates of childhood cancer mortality in India by enhanced verbal autopsies on a cohort of >27,000 pediatric deaths examined as part of the Million Death study, a mortality rate of 37% (95% CI: 31–42) per million population per year was obtained. This was more than many prior estimates of mortality. Disparities between mortality estimates were the widest in northeast India and for brain tumors [16]. Pediatric oncology in India still needs concerted, collaborative, and multidimensional efforts to reach international standards.

4 Challenges in the Management of Childhood Cancers in LMICs

The improvement in survival in pediatric cancers has been a paradigm where scientific advances in diagnosis, treatment, and supportive care have improved survival rates in many cancers; for example, in the UK, from <5% for childhood leukemias in the early 1980s to 80% by 1996–2000 [17]. The benefits obtained from these advances, resulting in remarkable improvements in survival in developed nations, have not translated into the same in LMICs with no narrowing of survival gap over time. Many factors contribute to the differences in outcomes, ranging from accessibility, availability, and acceptability of diagnostics and services to the advanced stage at presentation in resource-constrained areas. With the emergence of new evidence and collaborations worldwide, efforts to bridge this gap have been initiated aimed at delivery of cost-effective and adapted interventions with a tiered approach, identifying health delivery platforms of varying capabilities (primary health-care centers, district hospitals, specialist and teaching hospitals) to implement the varying intensities of treatment. The following are the main challenges faced in the treatment of childhood cancers in resource-constrained settings [11]:

Underdiagnosis The nonspecific manifestations of childhood cancers, especially hematolymphoid malignancies like leukemias and lymphomas, which can mimic infectious processes coupled with inadequate access to health-care delivery services, limited infrastructure, training, manpower resources, and service delivery networks, hamper the diagnosis of these malignancies. These limitations in diagnostic technology affect the diagnosis of childhood solid tumors far more, resulting in gross underdiagnosis.

Missed Diagnosis and Delayed Diagnosis The limitations as detailed above also contribute to missed diagnosis and delay in diagnosis, thereby hampering the timely delivery of treatment and affecting outcomes.

Inadequate Health-Care Infrastructure and Access to the Same There is a glaring deficit in the infrastructure needed to deliver proper and adequate services starting from the health delivery platforms available in LMICs. Childhood cancers require specialized diagnostic and treatment facilities, which also have the potential to take care of the anticipated specific complications in this vulnerable cohort. There is a lack of buildings, trained personnel (both medical and nonmedical), diagnostic modalities (including laboratory services, trained pathology, imaging services), and therapeutic services (chemotherapy, radiotherapy, surgery). Many sub-Saharan African countries lack any radiation unit; other countries have one unit per five million people, which restricts the delivery of one of the important treatment modalities for cancer [18]. The quality of chemotherapy drugs and their sustained availability is an issue in the continued delivery of care.

Lack of Supportive Care The paucity of sufficient supportive care networks, mainly addressing infection control and nutrition, precludes the use of the latest and best curative treatments in LMICs. Administration of chemotherapy with its attendant myelosuppression and infections can lead to increased morbidity and mortality in resource-constrained settings.

Dearth of Blood Products and Transfusion Support The successful treatment of childhood cancers, especially hematolymphoid cancers that constitute the bulk, requires a concrete transfusion support program, adequate number of blood donors and blood product units, and safety from transmissible diseases. A high seroprevalence of human immunodeficiency virus (HIV) and hepatitis B, especially in LMICs, reaching 10–25% among blood donors in Africa, warrants a hemovigilance system to monitor and improve the safety of transfusions [19]. Only 13% of LMICs have a national hemovigilance system, and only 53% of blood donations are appropriately screened [11, 20].

Malnutrition The prevalence of malnutrition is extremely high in LMICs, reaching 50–70% in some regions, and is associated with the inability to deliver dose-appropriate treatment, treatment interruptions and delays, increased toxicities (infectious and otherwise), and decreased survival [19].

Financial Constraints The delivery of the best contemporary treatment protocols requires financial support, which is otherwise unaffordable to the uninsured, lower-socioeconomic strata. Out-of-the-pocket expenditures, in addition to the treatment costs, incur additional financial burden on these families, as many of these health-care services are available at regions distant to their native places.

Treatment Refusal and Abandonment This is a real and concerning issue in many LMICs and is one of the major causes of treatment failure. The reasons for abandonment are multifactorial, with financial, social, and cultural causes. In an online survey conducted to assess the global frequency burden of this problem, 23,854 (15%) of 155,088 children, who were <15-years-old and newly diagnosed with cancer annually, were found to abandon therapy [21]. Approximately two-thirds of LMICs had median treatment abandonment ≥6%, but treatment abandonment ≥6% was reported in high- (9%), upper middle- (41%), lower middle- (80%), and low-income countries (90%, $p < 0.001$). Treatment abandonment may account for at least a third of the survival gap between HICs and LMICs.

A holistic support system consisting of the hospital team, nongovernmental organizations (NGOs), and governmental organizations along with a prospective tracking system were instrumental in reducing abandonment in a resource-constrained setting at the pediatric oncology department of Tata Memorial Hospital [22]. The annual rate of abandonment was reduced from 20% to around 5% [22] with these interventions.

Belief in Traditional and Complimentary Medicines Traditional healers have an increasingly recognized role in the communities in LMICs where the cultural beliefs and dependence on these medicines alone can lead to a delay in the diagnosis and treatment of curable cancers. A systematic review performed by the traditional and complimentary medicine Collaborative of the SIOP found that its median use during childhood cancer care is significantly higher in LMICs (66.7% ± 19%) compared with HICs (47.2% ± 20%), ($p = 0.02$) [23, 24]. The simultaneous undisclosed use of these medicines along with allopathic treatment can have hazardous consequences due to drug interactions and toxicities.

Lack of Palliative and Survivorship Care Palliative care is a core component of health systems, especially cancer care, which is lacking or underpowered in many LMICs. In LMICs, pain management is available in <50% of pediatric oncology units and high-potency opiates and adjuvant medications are available in <15% of these countries [25].

Moving forward, bridging the survival gap and addressing the above issues is being contemplated and is initiated by many committed stakeholders, and this collective engagement would go a long way in improving childhood cancer care and outcomes in LMICs. The World Health Organization (WHO) Global Initiative for Childhood Cancer was announced in 2018 with the aim of attaining 60% 5-year overall survival for children with the six most common childhood cancers globally by 2030, by providing governments with a technical package to scale up capacities and to expand and sustain them with support from global partners [26]. This is a key development in ironing out the inequity in health-care services across the globe and is a major drive toward attainment of WHO's Sustainable Development Goal (SDG) target of 3.4, which is to reduce premature mortality from noncommunicable diseases by one-third by 2030 [27].

Some of the steps put forward and implemented to scale up the childhood cancer services are detailed below [11]:

Tiered Health Service Delivery, Capacity Building, and Intervention Packages Identifying health delivery platforms (primary health centers, community health centers, district hospitals, specialist hospitals), strengthening health care in these systems, and integration of childhood cancer care into national health programs are the essential initial steps. A trained multidisciplinary medical and nonmedical workforce can be recruited in centers with varying capabilities such that satellite centers in greater numbers and better access to people in remote areas can deliver some aspects of treatment and supportive care, helping out families while dedicated higher-tier treatment centers, concentrated in resources and expertise, can deliver more complicated therapy. There should be increased access to medicines and technology and quality control to ensure the optimum continued delivery of treatment. The simultaneous integration of cancer care in essential benefits packages is the need of the hour to ensure equal benefits for all strata and to reduce abandonment.

Governance National cancer control programs and governing bodies should be developed and facilities and providers should be accredited.

Cancer Awareness There should be efforts to create awareness among the general public and general practitioners about the symptoms and diagnostic facilities available so that timely referral and treatment can be initiated. As a step toward this goal, the Pediatric Hematology Oncology (PHO) chapter of the Indian Academy of Pediatrics (IAP) initiated a National Training Program in Practical Pediatric Oncology (NTP-PPO) to train doctors, mainly in non-oncology centers.

Financing Both direct and indirect costs of treatment are an important deterrent to the initiation and continuation of therapy and hence should engage both the government and nongovernmental organizations and philanthropic support to ensure continued care and prevent abandonment. Government-supported health packages like the Ayushman health insurance scheme in India exemplifies this effort, thus limiting financial burden on the caregivers.

Twinning Programs Institutional and national collaborations open up opportunities for improvement in services, education, and research, and these exchanges have far-reaching consequences in improving outcomes on short- and long-term bases.

Health Information The development of cancer registries and inclusion of childhood cancers in them should be made mandatory, and these should be linked to regional and national databases of deaths to capture survival data. Vital statistical systems of the nations should also be strengthened as these data inform and guide the current and future policies.

Cost-Effective and Adaptive Treatments Local adaptation of treatment protocols must be done as per the evidence, to ensure maximum benefit with minimum morbidity and mortality due to treatment per se. This is important as most of the children in LMICs have additional issues like malnutrition in a setting where communicable diseases are also prevalent and are the competing causes of mortality in these immunosuppressed patients on therapy. There are some differences in the biology of various malignancies between HICs and LMICs, which could favor the adaptation of such cost-effective or less toxic protocols. Some examples of indigenously developed protocols adapted to the settings like MCP 842 for lymphomas, MCP841 for ALL (developed in collaboration with NCI, USA), EFT-2001 for Ewing sarcoma [28], and OGS 2012 for osteosarcoma [29] are relatively less toxic with good outcomes in resource-constrained countries. Metronomic chemotherapy with its attendant benefits of wide availability, limited costs, oral administration, and little infrastructure needs can be part of the constraint-adapted regimens in these resource-limited settings, with the understanding that metronomics shall not be a substitute for standard treatments wherever deliverable [30, 31].

In summary, effective delivery of childhood cancer care requires a comprehensive study of the current practices, incidence, and survival estimates to inform policies and to implement and scale up services in resource-constrained settings, thus warranting concerted efforts from different walks of the government, national and international institutions, and community as a whole.

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Oncopathology

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Abbreviations

CSF	Cerebrospinal fluid
DCIS	Ductal carcinoma in situ
ER	Estrogen
FNA	Fine needle aspiration
FNAC	Fine needle aspiration cytology
FS	Frozen section
GMS	Gomori methenamine silver
H&E	Hematoxylin and eosin
HER2	Human epidermal growth factor receptor 2
IHC	Immunohistochemistry
IOC	Intraoperative consultation
ISH	In situ hybridization
LED	Light-emitting diode
LM	Light microscopy
LN	Lymph node
NBF	Neutral buffered formalin
NHL	Non-Hodgkin lymphoma
PAP	Papanicolaou stain
PAS	Periodic acid–Schiff
PR	Progesterone receptor
QA	Quality assurance
SOHD	Supraomohyoid neck dissection
SOP	Standard operating procedure
WSI	Whole slide imaging
ZN	Ziehl–Neelsen

1 Principles

The practice of surgical pathology primarily relies on an accurate and careful macroscopic gross examination of the excised tissue, followed by a more detailed histological examination of tissue sections, integrated with other relevant clinical details and ancillary techniques to arrive at a definitive diagnosis.

One of the primary challenges in cancer management is embarking on an accurate diagnosis in which the pathologist plays a pivotal role. A definitive diagnosis of any lesion identified clinically or radiologically rests solely on the histopathological assessment of the lesion. No matter how high the index of clinical suspicion is, the diagnosis of cancer is conclusively established only after a thorough histopathological examination, and, hence, the latter is considered as the gold standard.

Not many years ago was the time when a mere diagnosis of "benign" versus "malignant" was enough for patient management. That scenario is revamped now largely due to the central role of histopathological parameters and biomarker assessment in determining the therapy and the clinical outcomes. The task of a pathologist is to provide an accurate, comprehensive and an integrated diagnosis, elaborating the relevant points in terms of additional prognostic and predictive factors, apart from the traditional staging information of cancers. Even today, though histomorphology remains the key element in the tumour diagnosis, it is further supplemented by various ancillary techniques to provide additional prognostic and predictive aids. Now, the reality is that a histopathology report is the defining characteristic of not just the diagnosis, but, guiding the oncologists inpertinent patient management providing relevant prognostic and predictive information. This has eventually redesignated the role of "Pathologist" as a "Theranostic Oncologist."

In the past several decades, major innovation waves have impacted surgical pathological practice, gradually considering limitations of the morphology alone in cases with diagnostic dilemmas. First being the introduction of electron microscopy (EM) for ultrastructural study, which has provided an insight into the histogenesis of tumors and aided in the diagnostic workup of difficult neoplasms. Subsequently, immunohistochemistry (IHC), to study protein expression, gained tremendous response and has quickly become an

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indispensable part of the surgical pathology practice, thus enabling finer subclassification, differentiating histological mimics and for various biomarker studies.

With the advent of high-throughput molecular techniques, there has been a revolutionary change in the cancer diagnostics as reflected in the constant characterization of previously unrecognized tumor types or variants. In many primary sites, tumor classification is now largely molecular -based, each with its own characteristic biology and behavior to allow the most appropriate classification for therapeutic intervention, to determine prognosis and for research. Details, viz., the tumor type, grade, differentiation, invasion parameters, proliferation index, pathological stage, metastatic status, hormone and other target receptors' status, etc., are often integrated with the molecular marker studiess.

Lastly, digital pathology with adoption of whole slide imaging (WSI) is deeply getting ingrained in histopathology, and artificial intelligence (AI)-powered applications are progressively getting incorporated in routine diagnostics.

In order to accomplish maximum information out of the tissue excised or biopsied, the specimen must be adequately fixed, grossed, processed, and stained to enable generation of the final histological report with a comprehensive diagnosis, which is clinically relevant and useful. In the subsequent sections, we will discuss the technical aspects, viz., grossing, tissue processing, staining, microscopy and other ancillary techniques pertaining to general oncopathological practice.

2 Grossing

The most important and basic step in surgical pathology is grossing. The interpretation of gross lesions begins with the observation, which indirectly serves as a road map to sampling representative areas for histological evaluation.

A correctly and adequately grossed specimen provides information related to the diagnosis, margin evaluation, nodal status, pathological staging, and residual tumor/posttreatment response evaluation.

2.1 Basic Requirements of Dissection/ Grossing Room

- A well-illuminated and adequately ventilated room with a powerful exhaust system to eliminate tissue odors and formalin vapors
- Grossing tables with boards with basic stationary and surgical instruments, viz., scalpel blades, forceps, scissors, knives and a scale, gloves, cotton, comfortable chairs, a formalin tank, and a water sink
- Bone saw for grossing bone specimens
- Leak-proof specimen containers, shelves, and compacters
- Disposal bins
- Photography facility
- A first aid box

2.2 Receiving Specimens

The samples are received safely and securely in the "specimen-receiving room." The main tasks to be accomplished in this room include the following:

- To match the identification mentioned on the requisition form and the specimen containers, confirm the number of specimens/ containers received, to check whether appropriate clinical details are mentioned, and to assign a unique laboratory specimen identifier number
- To note the condition of the specimen at the time of receiving it (if in inadequate formalin or autolyzed)
- In case of any doubt/discrepancy in the specimens received, the concerned/referring clinician should be contacted.
- The specimen may be rejected in case of any major discrepancy, the criteria for which should be clearly mentioned in the laboratory standard operating procedures (SOPs).

2.3 Specimen Fixation

Good and prompt fixation of the specimen is the prerequisite for surgical pathology. Cold ischemic time should be less than 1 h. In case of an anticipated delay of surgical specimens to reach the pathology laboratory for fixation, these can be kept in a refrigerator at 4°. Of the many fixatives available, 10% neutral buffered formalin (NBF) is the most preferred for routine histopathology, IHC, and molecular pathology techniques.

- Specimens should be adequately fixed, with the volume of the fixative being at least 10 times that of the tissue.
- Small biopsies are fixed immediately, for approximately 4–6 h, whereas for big specimens, at least 8–12 h are recommended. Over- or underfixation of a tissue has a deleterious effect on further downstream techniques.
- Big resection specimens are inked, serially sliced, and packed with formalin-soaked cotton in between the slices to facilitate persistent and optimum formalin penetration to prevent tissue autolysis.
- Gross photography is an integral part of surgical pathology and should be preferably performed when the specimen is in a fresh state, especially for rare and unusual cases.

2.4 Grossing/Surgical Cutup

2.4.1 Orientation of Specimens

Specimen orientation is important in oncopathology for surgical margin status evaluation, providing a guide to the surgeons to revise the close/positive margin/s in future.

- Apart from small biopsies and specimens, which can be oriented by anatomic locations, like colon specimens, a majority need to be oriented by the surgeons and mentioned accordingly on the requisition form.
- Most of the specimens are oriented with sutures, for example, in breast lumpectomy, a short suture is usually placed superiorly and a long one laterally. Sometimes, the lesion is marked with the guide wire after mammography guided localization, especially in post-chemotherapy settings.
- Revised margins are commonly oriented mostly as ink away from the tumor. Margins sampled should be always mentioned, if shave (S) or radial (R) margins are taken.
- Specimens, which are unoriented, should be mentioned in the gross findings. In such cases, the closest margin should be sampled.

2.4.2 The General Principles of Grossing

Before the actual start of tissue dissection, reconfirming the patient's identification, patient/specimen type, specimen orientation, and measurement is essential.

Information on specimen receiving, fixation, and grossing date and time, along with the names of the pathologist and the technician, should be mentioned on the surgical pathology form.

2.4.3 Gross Description

A thorough and meticulous examination of the specimen and sampling the appropriate areas form the basic premise of grossing. The description should be concise but precise.

- A gross description of the primary lesion should include its distribution, contour, color, shape, size, and consistency.
  - Distribution—unifocal, multifocal, or diffuse type of lesion
  - Contour—the relationship of the lesion with respect to the adjacent tissue and whether proliferative, infiltrative, or a flat lesion
  - Shape—ill-defined, circumscribed, or well-encapsulated
  - Apperance: Uniform/ variegated Necrosis - Present/ Absent Color—pale, brownish, hemorrhagic or blackish, pigmented
  - Consistency—soft, firm, or hard
  - Size—exactly three dimensions, with mention of the depth of invasion in cases with an infiltrative component
- The status of the adjacent tissue or any other secondary pathology, if present, should be mentioned.

2.4.4 Margin Evaluation

A surgical pathology report is incomplete without the mention of the status of the surgical margins.

There are two types of margins: shave face and radial/perpendicular. Shave margins have the advantage of being able to sample a larger area and are usually taken when the margins are grossly far away from the primary lesion (usually more than 1–2 cm away). However, the disadvantage seems to be higher chances of a false-positive margin, in cases with thick sections, and the inability to calculate the exact distance from the lesion microscopically.

On the other hand, radial margins, where a small portion of the tissue along with the lesion is sampled, prove useful in cases with close surgical margins for exact measurement of the microscopic distance of the margins from the lesion.

Usually, single black ink suffices if only one margin is sampled in one section. For cases with possible multiple margins in a single section, e.g., in Whipple's resection or vocal cordectomy specimen, different margins can be inked with different colors to facilitate their identification under microscopy.

2.5 Blocking Principles

2.5.1 Primary Lesion/Tumor

- A minimum of four sections from the main tumor, including sections with maximum depth and with an adjacent normal tissue. For certain tumors, like solid-cystic ovarian tumours, one section per centimeter of circumference is considered as optimum sampling.
- In case of an ill-defined lesion, additional sections may be submitted.
- In post-neoadjuvant treatment, the slice most representative of the tumor bed is submitted in a grid manner after matching with imaging.
- With multiples tumors, the intervening tissue is submitted.
- With large tumors with variegated appearance, multiple sections are submitted from grossly varied areas. Necrotic and hemorrhagic areas also need to be sampled.
- In solid cystic tumors, solid areas should be sampled adequately. In cystic tumour, areas with maximum cyst wall thickness should be sampled.

- Adequate evaluation of certain adjacent structures is critically important for pathological staging, e.g., skin involvement in breast tumors, pleura in lung resections, underlying bone in head and neck cancers, etc.

2.5.2 Margins

- All margins are labeled, mentioning the type of margin (radial or shave), and submitted separately one per block, with the inked surface guiding the embedding direction.

2.5.3 Adjacent Tissues

- Representative sections from the adjacent tissues should be submitted.

2.5.4 Lymph Nodes (LNs)

- All the lymph nodes, including those of the specimens as well as those sent separately, should be grossed and sampled entirely, unless it is grossly metastatic, wherein a single representative section is submitted.

2.5.5 Bone

- All the bony hard/calcified tissues should be decalcified using laboratory protocols before tissue processing.

3 Safety Precautions

All specimens must be considered a potential biohazard, and necessary universal safety precautions need to be followed with protective clothing, including good-quality masks, aprons, gloves, and goggles. Strict laboratory protocols need to be laid down and followed forthwith after the occurrence of any laboratory accident, e.g., sharp injuries, splash exposure, etc.

4 Staining

Following the series of tissue-processing steps, sections from the paraffin-embedded blocks are subjected to “staining.” This imparts color to an otherwise transparent tissue, thus enabling the pathologist to appreciate the morphological details under a microscope. It plays a crucial role in diagnostics and research settings.

The term “routine staining” in the histopathology laboratory refers to the conventional hematoxylin and eosin (H&E) stain, which is used for staining all tissue sections. Similarly, for cytological specimens, routine stains include Papanicolaou (PAP) stain, which is a combination of hematoxylin with Orange G 6 and eosin azure (EA) 50, whereas for hematological/bone marrow specimens, the most commonly used stains are Romanowsky stains (Wright and Giemsa stains). The term “special stains” refers to various other alternative stains that can be used as a diagnostic aid, in addition to routine staining to provide additional details. The term “advanced staining” refers to IHC or in situ hybridization (ISH), which stains the proteins and in situ DNA or RNA sequences, respectively.

4.1 Hematoxylin and Eosin (H&E) Staining

H&E staining is a basic and simple-to-use technique, which stains the nucleus and cytoplasm of a cell, including its extracellular components. This is the most frequently used stain in all the histopathology and some cytology laboratories for making a diagnosis, as it clearly highlights the underlying tissue morphology. The H&E stain has two dyes, which is a combination of hematoxylin, a basic dye (purplish-blue color, which stains acidic structures like the cell nucleus containing DNA and nucleoproteins as well as organelles that contain RNA, and eosin, an acidic dye (reddish or pink), which stains basic structures like the cytoplasm, cell wall, and extracellular matrix.

Automated staining machines and commercially prepared hematoxylin and eosin solutions are commonly used in modern laboratories for routine staining and form the most essential component of any histopathology laboratory.

4.2 Special Stains

Special stains include those that may be used to visualize specific tissue elements, or even microorganisms, which are not identified by H&E staining. In diagnostic pathology, common usage of special stains is now largely restricted to demonstration of organisms, viz., mycobacterium with Ziehl–Neelsen (ZN), fungus by Gomori methenamine silver (GMS) stain and periodic acid–Schiff (PAS) stain, and *Helicobacter Pylori* organisms with Warthin–Starry and Giemsa stains.

Traditionally, some of the special stains played a crucial role in diagnostic oncology, which have now largely been replaced by IHC. Some are still helpful adjuncts to tumor morphology, e.g., Fontana–Masson stain to demonstrate melanin pigment in a suspected case of malignant melanoma.

5 Frozen Section (FS)

Intraoperative consultation is a major responsibility of an oncopathologist and is considered as the most dynamic part of the practice. However, it is important to triage the specimens and not necessarily process them if there is no intent to modify the surgical procedure.

5.1 Basic Frozen Section (FS) Workflow

An unfixed tissue specimen reaches the FS station from the operation theatre accompanied by the requisition form mentioning the parameters that need to be assessed. The pathologist then grossly examines the specimen and submits representative sections for histological evaluation. These sections are then hardened by freezing in a cryostat (−20 to −30 °C), followed by sectioning (4–7-μm thickness), and subjecting them to staining. Rapid H&E staining and toluidine blue are the common stains used in FS. The approximate turnaround time is 20 min, from specimen receiving to the final FS diagnosis.

5.2 Indications

Broadly, the major indications for intraoperative FS that guide the surgical plan are

- Diagnostic
- Margin evaluation for the adequacy of surgical resection
- Lymph node (LN) status

5.3 Diagnostic

- To establish the nature of the lesion: benign vs. malignant
- To ascertain any clinically suspicious areas, which are unexpectedly encountered at the time of surgical exploration
- To evaluate the tumor grade, high- vs. low-grade, which determines the extent of surgery, e.g., for mucinous tumors of the colon
- Depth of invasion of the myometrial wall thickness
- To evaluate meticulously for any skip lesions in addition to the primary tumour mass in an excised specimen
- To determine the exact site of origin, primary versus metastatic in cases with multiple tumors

5.4 Margin Status

Adequacy of surgical margins is a pivotal prognostic and predictive parameter in big resection specimens in oncology, though the adequacy criteria differ and are based on the site affected.

It is necessary to mention the type of margin sampled (radial versus shave) and the exact microscopic distance of the tumor from the margin when close, even if the inked margin is technically free.

5.5 Lymph Node (LN) Status

LN status is one of the independent prognostic and predictive markers in oncology.

In breast carcinoma, sentinel LN status guides the axillary nodal dissection. In addition to the number of positive nodes, approximate nodal deposit size [if micrometastasis is (0.2–2 Mm) or macrometastasis is (>2 Mm)] and information on the extracapsular extension can be useful for making intraoperative decisions. Similarly, in head and neck cases, the nodal status of the contralateral side decides the level of neck dissection, supraomohyoid neck dissection, or modified neck dissection.

5.6 Frozen Artifacts and Limitations

Both the pathologist and the operating surgeon should be aware of certain limitations of the FS, which can lead to inaccurate diagnosis.

FS-related errors are classified as sampling, technical, or interpretative errors.

5.6.1 Sampling Errors

These errors are encountered due to inaccurate sampling carried out by the surgeon or grossing by the pathologists.

As in FS, most representative sampling is carried out and multiple sectioning is not feasible. This is especially important in encapsulated follicular neoplasms, wherein the malignancy criterion is capsular or vascular invasion, and in borderline ovarian neoplasms, wherein multiple sections are needed to rule out an invasive focus.

5.6.2 Technical Errors

As freezing is the medium of tissue hardening, a wide range of artifacts are commonly encountered, with the most common being tissue folds, improperly cut sections, especially of the fatty tissue, patchy and weak staining, and freezing artifacts obscuring the morphology, all of which can ultimately lead to diagnostic dilemma and interpretative errors.

5.6.3 Interpretative Errors

Poor differentiation of tumors, heterogeneity, varied and unusual morphologies and patterns, and sometimes crushing can lead to diagnostic difficulties, which need definitive characterization after paraffin processing and must be conveyed in the FS reports.

For a successful FS practice, knowing treatment algorithms with FS implications, effective communication, seeking a second opinion, and asking for an additional tissue, whenever required, would be a prudent approach.

6 Microscopic Techniques

A light microscope is the most essential part of a histopathology laboratory, which allows the microscopic evaluation of the target tissue at varying magnifications. The basic components of a light microscope include a light source, condensers, a body tube, an object stage, an objective, and an eyepiece.

The type and quality of the objective has the greatest influence on the microscope. Achromatic objectives are the most widely used for routine purposes. In most of the microscopes, the objective magnification powers range from 4× to 100× and the ocular magnification most commonly present is 10×. As a result, a standard microscope will provide a final magnification range of ~40×–1000×.

Depending upon the light path, transmitted light, or reflected light, different types of microscopic techniques exist, viz., bright-field, dark-field, phase contrast, interference microscopy, and polarized light microscopy.

The most commonly used technique is “bright-field” transmitted light microscopy for routine histopathological analysis of H&E, special stains, and IHC stains.

A polarizing microscope is a conventional microscope in which a polarizer and an analyzer is interposed and aligned, such that a birefringent object will appear bright against the dark background. This has many diagnostic applications in routine diagnosis, e.g., amyloid deposits in medullary carcinoma of the thyroid, etc.

Techniques dependent on the reflected light are fluorescence microscopy, confocal microscopy, and electron microscopy.

For fluorescence microscopy, different components like excitation, emission filters, a light source, a target tissue tagged with fluorophores, and a dichroic mirror are essential. It relies on the property of certain substances, which, when illuminated by light of a specific wavelength, will re-emit this light at a longer wavelength, which can then be visualized by the eyes. Fluorescence in situ hybridization (FISH) diagnostic tests make use of this technique.

Electron microscopy, although is diagnostic of certain neoplastic conditions, viz., demonstration of Birbeck granules in Langerhans cell histiocytosis, is not a preferred diagnostic modality due to the availability of superior and universal diagnostic techniques, viz., IHC. Moreover, the potential limitation of EM lies in the need for high cost of instrumentation, the level of technical expertise, and the stringent level of tissue processing. A confocal microscope is mainly utilized for research applications.

7 Cytology

The field of cytology has mainly two branches, viz., exfoliative cytology and fine needle aspiration cytology (FNAC).

Several factors play an important role in the evaluation of cytological specimens. The first and most important step is appropriate collection and handling of the specimens. Cancerous cells are often fragile, and, to identify these cells properly, they must be handled carefully during processing.

7.1 Types of Cytological Specimens

7.1.1 Exfoliative Cytology

Serous effusions, cerebrospinal fluid (CSF), urine, or samples that are forcibly removed, e.g., bronchial brushings, cervical, oral scraping smears

7.1.2 From a Lesion/Mass

Fine needle aspiration (FNA) and touch/imprint smears

7.1.3 Selection of Stains and Fixatives

The PAP stain is the most popular staining technique highlighting the crisp nuclear details. The most commonly used fixative is 95% ethyl alcohol.

The PAP stain slide should be combined with other stains like Giemsa and/or H&E, which highlight the cytoplasmic characteristics and are useful in highlighting various stromal features that are diagnostic of certain neoplasms.

7.2 Key Points in the Evaluation of Cytological Specimens

Before evaluating the cytological specimens, it is important to know how a cytological interpretation is different from an histological assessment. Especially in exfoliative cytology, abnormal cells are mainly discohesive with no stromal interface, a pattern-based approach to diagnosis is not always possible.

Smears are sometimes uneven, not with uniform thickness, with overlapping fragments, and enmeshed in the background material, thus leading to difficulty in evaluation. In addition, the relation of the lesion to the adjacent tissue cannot be ascertained in the cytological evaluation.

Scanty cellularity again poses diagnostic dilemmas, necessitating repeat evaluation in such cases.

7.3 Approach to Evaluation of Cytological Specimens

First and foremost, patient identification and rechecking the number mentioned on the requisition form and the smears should be performed.

A scanner view is used to assess cellularity and adequacy and then a low/high-power view is used for cytomorphological details, e.g., cell size, cellularity pattern, cell shape, nuclear features, cytoplasmic granularity, type of the stromal tissue and matrix, etc.

7.4 Cytology in Oncopathology: Interpretative Issues

Broadly, cytological assessment is helpful in oncological settings

- To identify and distinguish a benign tumor from a malignant one
- To further characterize the type of malignancy, such as carcinoma vs. lymphoma vs. sarcoma
- To differentiate high-grade from low-grade tumors, which is especially important in salivary gland tumors. To identify the metastatic nodal/ distant metastases

Although in majority of instances, cytological assessment helps in arriving at a definitive diagnosis, many scenarios do exist, which limits its diagnostic potential in cases, e.g., exact characterization of malignant small round cell tumors and further classification of differentiated thyroid follicular patterned neoplasms.

Nevertheless, ancillary techniques like IHC, EM, and molecular studies can be employed in such cases to aid in the final diagnosis. Moreover, cell block preparations from cytological specimens provide better material to perform various ancillary techniques over conventional smears.

8 Immunohistochemistry

IHC is based on the principle of antigen–antibody reaction for localizing specific antigens on cells in tissues. It has now become an important, valuable, and indispensable component of surgical oncopathological practice.

The first immunological method for diagnostic use was developed by Dr. Albert H. Coons in 1941, who officially launched the light microscopic (LM) IHC. However, only after the development of monoclonal antibodies in the late 1970s did the full-proof incorporation of IHC in pathology begin.

8.1 Applications

The applications of IHC can be classified further depending upon its utility as a diagnostic, prognostic, predictive, or genogenic marker.

8.2 Diagnostic

Usually, a panel of IHC markers are ordered, however, in an algorithmic manner

- Benign versus malignant lesions
- Classification of papillary lesions of the breast [papilloma versus papilloma with atypical features vs. papillary ductal carcinoma in situ (DCIS)] is largely dependent on the presence and absence of myoepithelial markers
- To differentiate prostatic carcinoma (especially if minute foci) from benign mimickers and precursor lesions
- Categorization of undifferentiated malignant tumors (carcinoma versus sarcoma versus lymphoma)
- Common scenario of soft tissue tumors
  - Malignant small round cell tumors (Ewing sarcoma versus Rhabdomyosarcoma versus Neuroblastoma versus poorly differentiated synovial sarcoma)
- Adenocarcinoma versus malignant mesothelioma
- To determine the primary site in cases with metastatic carcinoma
- Workup of hematolymphoid malignancy

8.3 Prognostic

- Hormone receptors [estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)] are prognostic markers in breast cancers.
- Tumors with a high proliferation index (Ki67) are high-grade and are associated with poor prognosis. In breast cancers, Ki67 is used as a surrogate marker for identifying luminal B subtype.

8.4 Predictive/Theranostic

The following are examples of biomarkers with predictive abilities

- ER/PR—Tamoxifen in breast cancer
- HER2—Anti-HER2; Trastuzumab in breast cancer
- CD20—Rituximab in B-cell NHL
- PD-L1—Immunotherapy

8.5 Genogenic

With so many molecular interventions in oncology, IHC is now increasingly being utilized to identify the underlying molecular abnormality, which further aids in diagnosis and guides patient management by identifying molecular therapeutic targets. This is a cost-effective and quick alternative to expensive molecular techniques.

- Identification of molecular alteration with the loss of IHC markers
  - Loss of integrase interactor 1 (INI-1) expression (surrogate for various molecular alterations affecting the INI-1 gene, including homozygous or heterozygous deletions, copy number alterations, epigenetic silencing, etc.) in SMARCB1 (INI-1)-deficient sinonasal tumor (diagnostic and prognostic)
- Identification of molecular alteration by the presence of protein expression
  - NUT protein expression (NUT gene rearrangement with BRD3 or BRD4) in NUT midline carcinoma (diagnostic and prognostic)
  - Anaplastic lymphoma kinase (ALK) protein expression (ALK gene rearrangement) in lung adenocarcinoma (predictive)
  - The presence of expression of the IDH-1 R132H mutation-specific antibody in gliomas (diagnostic and prognostic)
  - HER2 protein expression in >10% tumor cells with strong, intense, membarnaous staining pattern (HER2 gene amplification) in breast cancer (prognostic and predictive)

Although IHC has widespread applicability in the evaluation of tumors, its interpretation rests on clinical and morphological details and technical aspects. A well-preserved, fixed, and well-processed tissue is essential for optimal results of IHC. IHC does not work well with frozen and decalcified tissues and interpreting it as a true negative would be an error. Finally, it should be kept in mind that it is an adjunct to diagnosis and should be ordered and interpreted in an algorithmic pattern, considering possible clinical and morphological differential diagnoses.

9 Molecular Pathology

Molecular techniques represent a powerful strategy for screening, early detection (e.g., cancer of the cervix), tumor classification (e.g., breast cancer), monitoring efficacy of intervention, and unraveling disease mechanisms (e.g., hematolymphoid malignancies). Discoveries in our understanding of the molecular basis of disease are opening new avenues to new treatment modalities, as is evident from advances in the treatment of lung cancer. Molecular techniques, viz., polymerase chain reaction (PCR), sequencing, in situ hybridization, droplet digital PCR, and next-generation technologies in conjunction with advanced biochemical methods, innovative fluidics, and electronics, are employed to address the need for robust, automated test systems in contemporary molecular diagnostics.

Examples

- Fluorescent in situ hybridization (FISH) for in situ visualization of varied genomic alterations, including gene amplifications, gains, gene rearrangements, translocations, deletions, etc. This technique is utilized in wide range of solid tumors, including carcinomas, sarcomas, and lymphomas for diagnostic, prognostic, and therapeutic purposes.

9.1 Diagnostic

- Morphologically similar looking tumors in a spectrum of malignant small round cell tumors like Ewing sarcoma and poorly differentiated synovial sarcoma can be differentiated by demonstrating *EWSR1* gene rearrangement in Ewing sarcoma vs. *SSX18* gene rearrangement in synovial sarcoma.
- PCR-based clonality analysis and T- and B-cell gene rearrangement studies are helpful in distinguishing reactive lesions from lymphomas and further subtyping the lineage of lymphomas, whether B cells or T cells.

9.2 Predictive

Non-small cell lung carcinoma (NSCLC) with *ALK* gene and reactive oxygen species (*ROS*) gene rearrangements respond to the ALK and ROS TKI (tyrosine kinase inhibitors), respectively and breast cancers with HER2 gene amplifications respond to anti-HER2 agents.

Sanger sequencing is used to detect changes and alterations in the DNA sequence like, single nucleotide variants, point mutations, frameshift mutations like indels, complex mutations, etc. Gastrointestinal stromal tumor (GIST) patients with KIT exon 9 mutations receive 800 mg once a day (OD) of imatinib and patients with exon 11 mutations receive 400 mg OD. BRAF and MEK inhibitors targets tumours, like melanomas with a *BRAF V600E* substitution mutation.

9.3 Prognostic

A neuroblastoma with MYCN gene amplification connotes poor prognosis. Multiplex ligation-dependent probe amplification (MLPA) to study DNA copy number alterations is employed in neuroblastomas to demonstrate recurring genetic alterations affecting multiple chromosomes, including losses of the 1p, 3p, 4p, and 11q and/or gains of 1q, 2p, and 17q, which further supplement prognostic information, in addition to the MYCN status.

Next-generation sequencing testing is a massive, high-throughput parallel sequencing to detect copy number aberrations, single nucleotide variants, complex mutations, fusions, and the microsatellite instability status of multiple genes and encompasses an “all-in-one” test. This helps reduce the turnaround time in routine cancer management, e.g., in NSCLC cases.

10 Biorepository

With exponential developments in genomics and proteomics and greater emphasis on translational research, the need for human tissue samples to be used in translational research has grown. Therefore, safe and effective management of biospecimen banking services and biorepositories that store tissues for research use is the need of the hour. Contemporaneously, the ethical and regulatory environment for using human tissues in research has also become increasingly complex. Well-organized biorepositories that practice standardized methods for collection, long-term storage, retrieval, and distribution of specimens with sound ethical principles are an appropriate response to this situation, ensuring that the rights and interests of specimen donors/patients are protected and also that important research can proceed with high-quality, research-grade biospecimens. It provides a greater understanding of the disease and helps answer important questions about why cancer develops, how it grows, and who is at risk.

Large pathology departments located at tertiary cancer centers are in a vantage situation to establish bioresource centers by undertaking various tasks, e.g., operational, administrative, and legal/ethical tasks involved in the running of a successful biorepository.

11 Digital Pathology

Whole slide imaging (WSI), an emerging tool in diagnostic pathology, involves scanning of a glass slide and converting digital information into a virtual slide. WSI has been successfully utilized for primary diagnosis, secondary consultation (peer-to-peer case review or expert opinion), intraoperative consultations (FS diagnosis), remote diagnosis, quality assurance (QA), multidisciplinary interactions (e.g., tumor boards), and patient consultations.

The concerns limiting the regular usage of digital pathology (DP) in routine practice include the exorbitant cost of the setup, including high-quality slide scanners, high-resolution monitors, and data storage and security. The need for high-speed Internet connectivity cannot be underestimated in DP. However, with technological refinement, improvement in connectivity, and high-resolution imaging, pathologists have now gradually incorporated the usage of digital microscopy even for the purpose of primary diagnosis.

In a vast country like India, the utility of WSI can have an immense impact, wherein opinions can be sought by underprivileged centers with limited resources, manpower, and expertise from tertiary care institutions with better expertise.

11.1 Digital Pathology and Artificial Intelligence

Adoption of WSI and the resultant generation of digital histopathological images has led to the increased interest and demand for their analysis, such as computer-aided diagnosis using machine learning and deep learning techniques.

Powerful artificial intelligence algorithms with constellation of histopathological images, genomic data, and clinical/radiological data can be utilized to make predictions about the evolution of tumors and would allow treatment to be precise and personalized in its true sense.

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Oncological Hematopathology

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Abbreviations

aCLL	Atypical chronic lymphocytic leukemia (CLL)
AITL	Angioimmunoblastic T-cell lymphoma
ALCL	Anaplastic large cell lymphoma
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ASO	Allele-specific oligonucleotide
ATLL	Adult T-cell leukemia/lymphoma
B-ALL	B-cell acute lymphocytic leukemia
BCP-ALL	B-cell acute lymphoblastic leukemia/lymphoma
BL	Burkitt's lymphoma
BM	Bone marrow
BPDCN	Blastic plasmacytoid dendritic cell neoplasm
B-PLL	B-cell prolymphocytic leukemia
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CRLF2	Cytokine receptor-like factor 2
CSF	Cerebrospinal fluid
ddNTP	Dideoxynucleotide triphosphate
DI	DNA index
DLBCL	Diffuse large B-cell lymphoma
ET	Essential thrombocythemia
FBS	Fetal bovine serum
FC	Flow cytometry
FCI	Flow cytometric immunophenotyping
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
FNA	Fine needle aspiration
FSC	Forward scatter
HCL	Hairy cell leukemia
Ig	Immunoglobin
LAIP	Leukemia-associated immunophenotype
LPL	Lymphoplasmacytic lymphoma
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndromes
MF	Mycosis fungoides
MN	Myeloid neoplasm
MPN	Myeloproliferative neoplasm
MPO	Myeloperoxidase
MRD	Minimal residual disease
MZL	Marginal zone lymphoma
NGS	Next-generation sequencing
NSE	Neuron-specific enolase
PAS	Periodic acid–Schiff
PCR	Polymerase chain reaction
PMF	Primary myelofibrosis
PV	Polycythemia vera
RFLP	Restriction fragment length polymorphism
RQ	Real-time quantitative
RQPCR	Real-time quantitative PCR
RT	Reverse transcriptase
sIg	Surface immunoglobulin
SS	Sezary syndrome
SSC	Side scatter
T-ALL	T-cell acute lymphoblastic leukemia/lymphoma
TCR	T-cell receptor
T-PLL	T-cell prolymphocytic leukemia
WBC	White blood cell
WHO	World Health Organization

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1 Introduction

Modern hematopathology practice employs a systematic approach in order to render a diagnosis that is clinically appropriate, evidence-based, and serves as a guide toward personalized medicine. It involves careful morphological study of the peripheral blood, bone marrow aspirate, followed by classification of the neoplasm according to the immunophenotype. Finally, molecular testing is an integral part of the present-day test battery, as the World Health Organization (WHO) 2017 [1] classification mandates classifying neoplasms according to their recurring genetic abnormalities, to guide appropriate treatment. This chapter discusses the essential aspects of a hematopathology laboratory, specialized in hemato-oncology, an overview of the techniques used, and the applications in various hematolymphoid neoplasms.

2 Organization and Elements of a Hematopathology Laboratory

A hematopathology laboratory is comprised of different specialized sections, encompassing the various stages of sample processing and diagnosis. Once a sample is received, it undergoes a myriad of processing methods, which include the following in order:

2.1 Sample Processing

- **Slide preparation and staining**: Morphological evaluation of the bone marrow aspirate slides requires adequate slide preparation and staining with one of the Romanowsky stains (e.g., Wright, Giemsa, Leishman).
- **Processing for flow cytometric evaluation**: This includes different protocols like "lyze–stain (staining with the antibodies)–wash" or "stain–lyze–wash", including permeabilization for cytoplasmic markers.
- **Pre-PCR (polymerase chain reaction) processing for molecular tests**: First, the erythrocytes are lyzed and the nucleic acids—DNA and RNA—are extracted using manual or automated kit-based techniques.
- **PCR**: The template DNA extracted is exponentially amplified using specific primers. The RNA is reverse-transcribed to complementary DNA (cDNA) and then further processes are carried out. The various applications of PCR are discussed in detail in the section "Molecular techniques."
- **Library preparation for next-generation sequencing (NGS)**: Library preparation is the single most important component of a next-generation sequencing test. Adequate amplification and target enrichment with addition of unique molecular barcodes are important basic steps for the same.

2.2 Analysis

- **Morphological evaluation**: Specialist hematopathologists perform careful morphological analysis of the bone marrow aspirate slides, which involves the percentage of abnormal cells, the morphology, and additional information on subtle diagnostic clues, all of which help in further characterization of the disease and guide further immunophenotypic and molecular analyses.
- **Flow cytometry**: Flow cytometric output data and plots are analyzed using sophisticated software, which help in visual identification of the expression of various antigens of the cells of interest. The analysis and final disease characterization is performed by specialist hematopathologists, based on the recommendations of the WHO.
- **Molecular techniques**: The raw NGS data are run through sophisticated bioinformatics pipelines specifically designed for different assays. The output data are then analyzed by molecular pathologists to differentiate pathogenic from nonpathogenic mutations. The implications of the detected genetic variants are derived from thorough literature search, and, finally, a wholesome evidence-based report is provided to the treating physician.
- The other disease-specific tests conducted include real-time monitoring of BCR-ABL1 copy numbers in chronic myeloid leukemia (CML) patients and promyelocytic leukemia/retinoic acid receptor alpha (PML-RARA) in acute promyelocytic leukemia patients, donor status in bone marrow transplant recipients, clonality studies, and so on, which are discussed in detail further.

3 Collection, Transport, and Processing of Samples

Proper sample collection, transport, storage, and appropriate processing are important preanalytical components of hematological testing. The samples that can be collected for evaluation of a hematolymphoid neoplasm include:

- Peripheral blood
- Bone marrow
- Fine needle aspirates
- Body fluids (e.g., pleural, peritoneal, cerebrospinal fluid (CSF), saliva, buccal swab)

- Solid tissue samples need to be isolated as single suspension by mechanical (slicing, mincing, and teasing using appropriate devices) or enzymatic methods (trypsinization).
- Bone marrow aspirate slides—in specific circumstances, like unavailability of an adequate sample, DNA can be extracted from stained or unstained bone marrow aspirate slides also.

The type of sample, quality, quantity, and anticoagulant used all play key roles in the reliability and accuracy of any test, which is to be performed. For immunophenotypic analysis and molecular techniques, the conditions recommended are discussed below.

3.1 Flow Cytometry

For peripheral blood and bone marrow aspirates, fine needle aspiration (FNA) samples need to be anticoagulated using ethylenediaminetetraacetic acid (EDTA) or heparin and should be analyzed within 24–48 h. Samples like CSF, which degrade rapidly, need to be analyzed within 1 h of collection. In case of any delay in sample processing, the samples need to be stored in stabilization media, e.g., homemade media containing Roswell Park Memorial Institute (RPMI) and 5% fetal bovine serum (FBS) or commercial media like TransFix (Cytomark, UK) [2].

Once the sample is received in the laboratory, the antigens to be tested on that particular sample are determined by integration of information like clinical history, morphological evaluation of cells, other laboratory findings, and any previous flow cytometry (FC) findings.

3.2 Molecular Techniques

EDTA is the preferred anticoagulant for the collection of whole blood and bone marrow specimens [3]. A total of 5 mL of peripheral blood is usually adequate at the diagnostic time point [if the total white blood cell (WBC) count is not low], but a minimum of 10–20 mL is recommended for follow-up samples [4].

If needed, sample transport should be carried out in compliance with the norms of the International Air Transport Association [3].

Blood scheduled for DNA analysis can be stored at room temperature for up to 24 h or at 2–8 °C for up to 72 h prior to DNA extraction. Blood scheduled for cellular RNA analysis should be collected in a tube containing an RNA-stabilizing additive [3]. It is generally accepted that samples should be processed for RNA extraction as soon as possible. Reliable quantification is not possible from a follow-up sample older than 72 h [4].

Once isolated, DNA is stable at 2–8 °C for at least 1 year. Purified RNA is best stored as a precipitate in ethanol at −70 °C or lower [3].

4 General Techniques

The general techniques employed in a hematopathology laboratory are described.

4.1 Cell Counts, Morphology, and Cytochemistry

A complete blood count including a seven-part differential of the WBCs is obtained by automated analyzers; blast count is further confirmed manually. The blood and bone marrow aspirate slides are prepared and stained using Romanowsky dyes for proper evaluation. The slides are evaluated under a microscope, and a manual 500 cell differential is performed by trained pathologists. Special stains and cytochemistry are used for demonstrating the iron stores, myeloperoxidase (MPO) positivity, and neuron-specific enolase (NSE) positivity. Other special stains like periodic acid–Schiff (PAS) can also be used.

4.2 Red Cell Lysis

Both flow cytometry and molecular techniques use white blood cells (WBCs) as the cells of interest. Therefore, red cells are lyzed before processing for these tests. Red blood cell (RBC) lysis is performed using an ammonium chloride-based lysis buffer and, then, the nucleic acids are extracted.

5 Flow Cytometry

Flow cytometric immunophenotyping (FCI) is an integral part of an investigation of hematological neoplasms and it helps in the diagnosis, classification, prognosis, and monitoring of the treatment response.

5.1 Principle

Flow cytometry (FC) is both a qualitative and quantitative technique that deals with the measurement of cells in suspension, where the cells are made to flow in a single line one after the other (laminar flow) with the help of hydrodynamic focusing (using isotonic sheath fluid). Cells from peripheral blood, bone marrow, serous cavity fluids, cerebrospinal fluid, and solid tissues (obtained by fine needle aspiration cytology or teasing the tissue biopsy) can be analyzed in terms of size, internal complexity, antigens present on the cell membrane surface and/or intracellular components (using fluorescent-labeled antibodies), and DNA and RNA content using multiparameter FC [5]. Cells in the sample analyzed are thus assigned particular lineage and maturity status (progenitors or mature cells) depending on the antigens they express, which can be used to arrive at a diagnosis.

5.2 What Happens Inside a Flow Cytometer?

An individual cell going through the laminar flow strikes the laser beam and scatters laser light in different directions. One part of the light, at a low angle along the axis of the laser beam, is in proportion to the cell size and is known as forward scatter (FSC), whereas another part of the light gets scattered at a right angle, which is in proportion to cell complexity (determined by cell granularity and nuclear characteristics), and is known as side scatter (SSC). Based on these scatter properties, the nature of the cell being analyzed can be accurately determined.

Laser light also excites fluorochrome dyes conjugated with monoclonal antibodies attached to respective antigens on the cell, resulting in the emission of fluorescent light of particular wavelength [6]. This is further separated by a series of optical filters and mirrors and is measured by individual detectors, resulting in the generation of electronic data, which are analyzed by FC software. Depending on the capacity to measure a number of fluorochromes simultaneously, flow cytometers are usually categorized as 6-color, 8-color, 10-color, etc.

5.3 Indications

The Bethesda International Consensus Conference (2006) on the flow cytometric immunophenotypic analysis of hematolymphoid neoplasia has enlisted clinical finding-based indications, as follows [7]:

- Cytopenias
- Leukocytosis
- Detection and subtyping of blasts/atypical cells in peripheral blood and bone marrow and body fluids
- Evaluation of lymphocytosis
- Plasmacytosis
- Lymphadenopathy

5.4 Additional Indications

- Assessment of response to therapy [minimal residual disease (MRD) monitoring]
- Evaluation of prognostic markers
- Enumeration of CD34$^+$ stem cells for stem cell transplantation
- Tumor proliferation index (e.g., Ki67$^+$ tumor cells)
- T-cell clonality assessment (T-cell receptor Vβ repertoire analysis, e.g., in eosinophilia)
- Detecting potential therapeutic targets
- Immune cell profiling assays (T-cell subset enumeration)
- DNA analysis (ploidy, proliferation, i.e., S phase, apoptosis)
- Human leukocyte antigen (HLA) typing
- Cell function studies (e.g., T-cell function)
- RNA detection studies (reticulocytes count)

Suspected patients with hematological malignancies with findings like mature neutrophilia, polyclonal hypergammaglobulinemia, polycythemia, thrombocytosis, and basophilia may not benefit from flow cytometric immunophenotyping (FCI) analysis right now [7].

Common immunophenotypic markers used for diagnosis of hematolymphoid neoplasms are enlisted in Table 1.

5.5 An Overview of Immunophenotypic Analysis of Hematolymphoid Malignancies

5.5.1 Acute Leukemia

Acute leukemia is the most common group of hematolymphoid neoplasms of the pediatric population and constitutes a major group in the adult population as well. The primary step in the diagnosis of acute leukemia is to assign the lineage. Immunophenotyping has come to play an integral role in the enumeration of leukemic populations, assignment of lineage, identification of prognostic subgroups, and subsequent post-therapeutic monitoring [8]. Blasts are abnormal precursors, identified on the basis of their characteristic expression of antigens of immaturity like CD34, CD117, and the absence or decreased levels of maturation antigens. Usually, blast cells show low SSC and dim/absent levels of CD45 expression along with aberrant expression of antigens in the form of lineage infidelity (such as myeloid markers on lymphoblasts or lymphoid markers on myeloblasts). In few cases, leukemic cells express antigens of more than one lineage, making it impossible to assign any one lineage with certainty, which is referred as “ambiguous lineage” [9]. The immunophenotype provides fundamental information to accurately stratify patients and initiate an appropriate therapy.

Table 1 Common antigens used in FCI

Cells	Lineage-associated antigens	Other antigens
Pluripotent stem cells	CD34, CD133	dCD45, CD117, CD123, HLADR
Myeloblasts	MPO, CD117, CD13, CD33, CD15, CD11b	CD34, CD38, dCD45, HLADR
Monoblasts	CD14, CD13, CD11b, CD11c, CD33, CD36, CD64, CD65, CD66, lysozyme, CD86	CD34, CD38, dCD45, HLADR
B lymphoblasts	CD19, cyto/sCD22, cytoCD79a, vCD20	CD10, CD34, dCD45, CD24, CD38, HLADR, nTdT
T lymphoblasts	Cyto/sCD3, CD1, CD2, CD4, CD5, CD7, CD8	vCD10, CD34, dCD45, HLADR, nTdT
Granulocytes	vCD13, vCD11b, bCD15, vCD16, CD33, CD66	vCD10, CD38, mCD45
Monocytes	CD4, CD14, CD13, CD11b, dCD15, bCD33, bCD64, CD68, dCD123, lysozyme	bCD36, CD38, bCD45, HLADR
Basophils	CD13, CD33, bCD123	dCD22, CD38, mCD45,
Eosinophils	CD11a, CD13	CD38, bCD45
Mature B cells	CD19, CD20, CD22, cyto79a, CD79b, surface kappa, surface lambda	CD27, CD38, bCD45, HLADR
Mature T cells	CD2, CD3, CD4, CD5, CD7, CD8, vCD56, vCD57	bCD45
NK cells	CD2, cytoCD3, CD7, vCD8, CD16, CD56, vCD57, CD94, CD158, CD161	bCD45, CD38, HLADR
Plasma cells	CD138, bCD38, CD19, bCD27, CD319, CD229, cyto79a, cyto-kappa, cyto-lambda	dCD45
Erythroid cells	CD235a, CD105, (RBCsCD55 and CD59)	bCD36, bCD71, CD203c
Platelets	CD41, CD42, CD61	–
Dendritic cells	CD123, CD304, CD303	HLADR
Mast cells	bCD117, CD33, CD203c	

b bright, *v* variable, *m* moderate, *d* dim

5.5.2 Acute Lymphoblastic Leukemia (ALL)

Acute lymphoblastic leukemia (ALL) is one of the commonest malignancies in children and accounts for around 20% of acute leukemia cases in adults [10, 11]. Flowcytometric immunophenotyping and DNA index (DI) assessment play a pivotal role in ALL both at diagnosis and during follow-up.

5.5.3 Precursor B-Cell Acute Lymphocytic Leukemia (B-ALL)

B-ALL comprises approximately 80–85% of ALLs [7]. The blasts cells in B-ALL typically express CD19, CD22 (surface and/or intracellular), CD79a (intracellular), CD10 (known as the common ALL antigen; CALLA), CD20 (in some cases), TdT (nuclear), CD34, HLADR, and variably dim to negative CD45 (Fig. 1). CD19 has the highest sensitivity for the detection of B-cell lineage [9]. In a few cases, they also aberrantly express myeloid antigens like CD13 and CD33. Antigen expression by ALL cells represents their degree of differentiation. The recent WHO classification of B-ALL has been based on underlying cytogenetic abnormalities. Recurrent cytogenetic abnormalities and associated immunophenotypes are described in Table 2 [12–15, 22–25].

A recent WHO (2017) [1] update on hematolymphoid neoplasms has also recognized two distinct high-risk entities of B-ALL as provisional categories, including BCR-ABL-like or Philadelphia (Ph) chromosome-like B lymphoblastic leukemia/lymphoma and B lymphoblastic leukemia/lymphoma with intrachromosomal amplification of chromosome 21 (iAMP21). Ph-like ALL is a high-risk subtype of ALL, and shows gene expression profiling similar to that of BCR-ABL-positive B-ALL with various types of chromosomal rearrangements, involving different genes and many partners [26]. Approximately half of the patients with Ph-like ALLs harbor overexpression of the cytokine receptor-like factor 2 (CRLF2) [27]. CRLF2 genomic rearrangements are strictly associated with its surface overexpression and adherence and is easily detected by FC [28]. B-ALL with iAMP21 is defined as a gain of at least three copies of part of chromosome 21 incorporating *RUNX1* and is usually recognized by fluorescence in situ hybridization (FISH) probes [29].

Normal B-cell precursors (hematogones) also express CD10, CD19, CD22, CD34, and variable CD20; however, they show typical and reproducible maturation stages with constant levels of antigen expression, which differ from B-ALL in one or more aspects. Hence, knowledge of normal B-cell precursors helps in identifying residual tumor cells in B-ALL [9]. In addition, hematogones do not show aberrant expression of myeloid antigens like leukemic cells do, making FCI successful in the detection of MRD in B-ALL.

5.5.4 Precursor T-cell Acute Lymphoblastic Leukemia/Lymphoma (T-ALL)

Detection of (cytoplasmic) CD3 expression is a tell-tale sign for T-cell lineage assessment. Other T-cell lineage markers are CD1a, CD5, CD7, and CD2. The antigens indicating the precursor nature of T-lymphoid blasts are TdT, CD99, and CD34. The majority of T-ALL show lack of CD4 and CD8 expression; however, co-expression of CD4 and CD8 can also be seen. A subset of the T-ALL cases expresses variable CD10. T-ALL blasts can also show aberrant myeloid antigen expression, e.g., CD13 and CD33.

According to the European Group for the Immunologic Classification of Leukemias (EGIL), T-ALL can be divided into the following subtypes: (1) pro-T ($cCD3^{+}$, $sCD3^{-}$, $CD1a^{-}$, $CD2^{+}$, $CD5^{-}$, $CD7^{+}$, $CD34^{-}$, $CD4^{-}$, $CD8^{-}$), (2) pre-T/immature ($cCD3^{+}$, $sCD3^{-}$, $CD1a^{-}$, $CD2^{+}$, $CD5^{+}$, $CD7^{+}$, $CD34^{-}$, $CD4^{-}$, $CD8^{-}$), (3), cortical T ($cCD3^{+}$, $sCD3^{+/-}$,

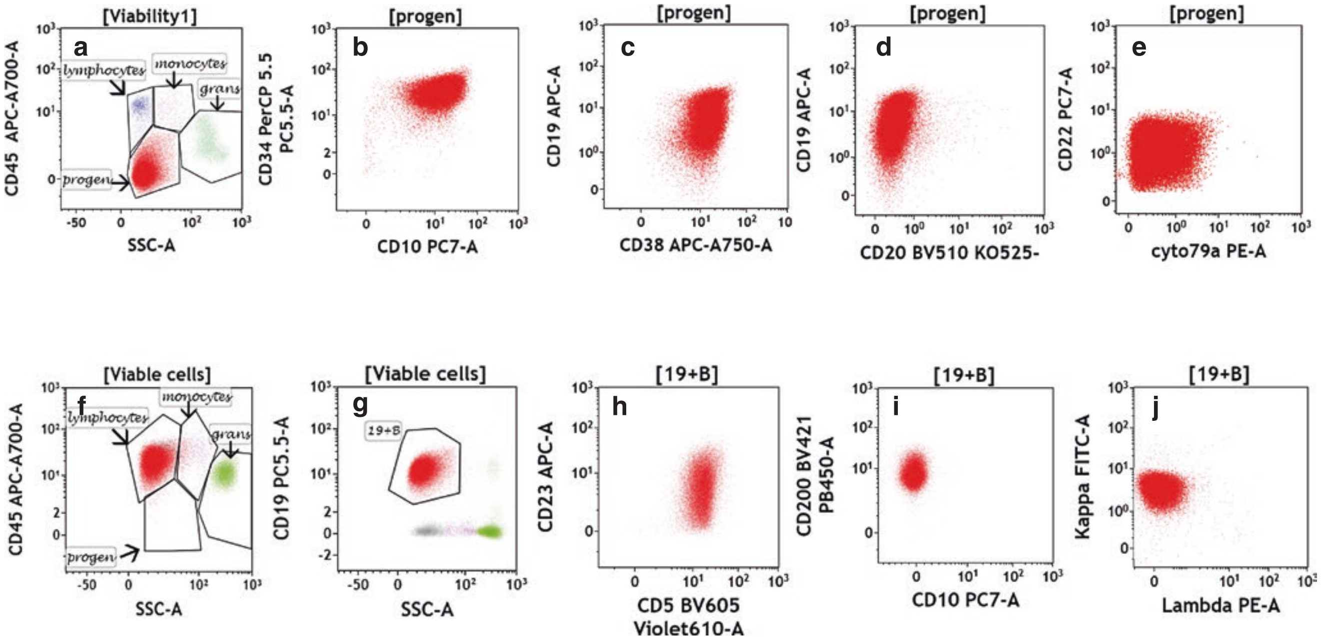

Fig. 1 Plots (**a**–**e**) represent a case of B-cell precursor lymphoblastic leukemia. Based on CD45 expression and SSC, WBCs are divided into lymphocytes, monocytes, granulocytes, and progenitors (**a**). Cells in the progenitor region are blasts and express dim CD45 (**a**), CD34 (immature marker) and CD10 (**b**), CD19 (B lineage-specific) and CD38 (**c**), are negative for the mature B marker CD20 (**d**), and express dim expression of CD79a and CD22 (**e**). Plots (**f**–**j**) represent a case of chronic lymphocytic leukemia. Based on CD45 expression and SSC, WBCs are divided in to lymphocytes, monocytes, granulocytes, and progenitors (**f**). The progenitor gate does not show any cells (**f**). Lymphocytes are gated with the help of CD19 to separate B lineage cells (**g**). These cells express bright CD45, CD5, CD23, and CD200 and are negative for CD10 (**h**, **i**). These cells are clonal and show kappa restriction (**j**)

Table 2 Acute leukemia with recurrent cytogenetics and their associated immunophenotypes

A. B-ALL with recurrent cytogenetics and associated immunophenotypes				
Recurrent cytogenetics	Morphology	Immunophenotype	Prognosis	References
B-ALL with t(4;11) *MLL/AF4* proB phenotype	No unique morphology distinguishing from other ALL types	CD10(N), CD15(D), NG2(P)	Poor	[10, 11]
B-ALL with t(12;21) *TEL/AML1*	No unique morphology distinguishing from other ALL types	CD13(P)	Favorable, few late relapses	[12]
B-ALL with t(9;22) *BCR/ABL*	No unique morphology distinguishing from other ALL types	CD13(V), CD33(V), CD25(P), CD10(B)	Poor	[13]
B-ALL with t(1;19) *TCF3/PBX1*	No unique morphology distinguishing from other ALL types	CD9(B), CD10(D)	Poor, CNS relapse	[14, 15]
B-ALL with hyperdiploidy	No unique morphology distinguishing from other ALL types	CD10(B), CD45(N)	Favorable	[9, 14]
B. AML with recurrent cytogenetics and associated immunophenotypess				
AML with t(8;21) (q22;q22); *RUNX1-RUNX1T1*	Large blasts with abundant basophilic cytoplasm, numerous granules, long thin slender auer rods, perinuclear Hof s. Granulocytic series show dyspoeisis	CD34(B), CD13(B), CD33(N/D), MPO(B), CD19(D), TdT(D), CD56(P/N)	Good KIT mutations and/or CD56 expression indicates adverse prognosis	[16, 17]
AML with inv(16) (p13.1q22) or t(16;16) (p13.1;q22); *CBFB-MYH11*	Myelomonocytic morphology, increased eosinophils of all stages of maturation and basophils	CD34(B), CD117(B), CD14(P), CD11b(P), CD4(P), MPO(P), CD2(P/N)	Good KIT mutations, older age, high white cell count, and *FLT3* mutations indicate adverse prognosis	[9, 18]
Acute promyelocytic leukemia with t(15;17) (q22;q12); *PML-RARA*	Hypergranular abnormal promyelocytes, faggot cells, hypogranular bilobed cells in a microgranular variant	CD34(N), HLA-DR(N), CD15(N/D), MPO(P), CD56(P/N)	Good CD56 expression indicates adverse prognosis	[19]
AML with t(9;11) (p22;q23); *MLLT3-KMT2A(MLL)*	Monoblasts and promonocytes	CD34(N/P), CD13(N), CD14(P/N), CD11b(P), CD4(P), MPO(P), CD19(N/P), NG2(P)	Intermediate MECOM overexpression associated with poor outcome	[9, 20]

B. AML with recurrent cytogenetics and associated immunophenotypess				
AML with t(6;9)(p23;q34); *DEK-NUP214*	Increased basophils; granulocytic and erythroid dysplasia	CD64(P), MPO(P), CD9(P), TdT(P)	Poor High frequency of *FLT3-ITD*	[9, 18, 20]
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-MECOM(EVI1)*	Dysplasia in all three series in bone marrow and peripheral blood neutrophils show Pelger–Heut anomaly	CD34(P), CD117(P), CD13(P), HLA-DR(P), CD7(P)	Poor	[20, 21]
AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*	Medium-to-large sized blasts, basophilic cytoplasm, blebs, bilobed blasts, micromegakaryocytes	CD61(P), CD41(P), MPO(N)	Poor	[9, 20, 21]
AML with *BCR-ABL* (provisional entity) CML and MPAL should be ruled out before diagnosing this entity	No characteristic morphology, lower peripheral blood basophilia compared to CML	CD34(P), CD13(P), CD33(P), CD19(P/N), CD7(P/N), Tdt(P), CD25(p)	Poor	[8, 21]
AML with mutated *NPM1*	Monoblasts, nuclear cupping in the blasts	CD34(N), CD14(P), CD64 (P), CD36(P), CD123(P)	Good presence of *FLT3-ITD* mutations indicate poor prognosis	[8]
AML with biallelic mutations of *CEBPA*	No characteristic morphology	CD34(P), CD13(P), CD33(P), CD15(P), CD7(P)	Good	[8]

B bright, *D* dim, *P* positive, *N* negative, *V* variable

CD1a$^+$, CD2$^+$, CD5$^+$, CD7$^+$, CD34$^-$, CD4$^+$, CD8$^+$), and mature/medullary-T (cCD3$^+$, sCD3$^+$, CD1a$^-$, CD2$^+$, CD5$^+$, CD7$^+$, CD34$^-$, CD4$^{+/-}$, CD8$^{+/-}$) [30]. Few studies have claimed a correlation between the stages of T-cell differentiation in T-ALL and survival [31]. However, with modern chemotherapy and MRD-based risk stratification, developmental stages lose their prognostic significance. A novel unique subgroup has been recently described as early T-cell precursor-ALL (ETP-ALL), which shows characteristic immunophenotypic features, like lack of CD1a and CD8 expression, weak CD5 expression, and expression of at least one myeloid and/or stem cell marker [32]. Patients with this form of leukemia had a high risk of remission failure or hematological relapse [32].

5.5.5 Acute Myeloid Leukemia (AML)

FCI plays a major role in the establishment of the myeloid lineage and illustrates the nature of differentiation such as granulocytic, monocytic, erythroid, or megakaryocytic. It also objectively provides information on associated dysplasia and helps in the diagnosis of AML with multi-lineage dysplasia [32]. Most importantly, a detailed immunophenotypic expression aids in the detection of MRD, which has a significant role in both prognosis and therapy.

Blasts in AML typically express dim CD45, CD34, and HLADR along with myeloid antigens like CD13, CD33, CD117, and cytoplasmic MPO and, less frequently, CD15, CD11b, and CD66 [9]. The expression of at least two monocytic antigens such as CD14, CD4, CD11b, CD11c, CD36, CD64, and CD68 and lysozymes is required to define the monocytic differentiation of blasts [18, 33]. Expression of CD235a (glycophorin A), CD71, and CD36 and lack of CD64 indicates erythroid nature. Similarly, CD41, CD61, CD42 (less frequently), and lack of CD34 and HLADR indicate the megakaryocytic nature (acute megakaryoblastic leukemia) [16, 18, 34].

The recent WHO classification of AML has mainly categorized AML on the basis of associated cytogenetics into a distinct group called AML with recurrent cytogenetics. The morphology, immunophenotypic expression, and prognosis associated with an individual subgroup of this category are all shown in Table 2 [13, 17, 19–21, 35–38].

5.5.6 Recently Described Immunophenotypic Subgroup in AML

A unique diagnostic immunophenotype (the RAM phenotype) in otherwise standard risk pediatric patients was described, which shows the absences of HLADR, CD38, dim-to-negative CD45, and bright CD56 with a high induction failure rate and extremely poor outcome [39].

5.5.7 Blastic Plasmacytoid Dendritic Cell Neoplasms (BPDCNs)

A BPDCN is an aggressive blastic neoplasm originating from plasmacytoid dendritic cells (PDCs) and is a separate entity in the current WHO classification [40, 41]. The blasts co-express CD4, CD56, and CD123 in association with other markers like CD2, CD5, CD303, CD7, CD13, CD33, CD68, etc. They are specifically negative for CD11c, CD14, CD34, CD117, and cytoplasmic MPO. One-third of cases show TdT positivity [40, 41].

5.5.8 Acute Leukemia of Ambiguous Lineage

According to the WHO-provided guidelines [10], lineage can be defined as follows:

- *Myeloid lineage*: Expression of MPO

In monocytic differentiation, at least two of CD11c, CD14, and CD64 and lysozyme antigens

- *B Lineage*: Bright CD19 along with bright expression of one or more of CD10 or cytoplasmic CD22 or CD79a

Dim CD19 with a bright expression of two or more of CD10 or cytoplasmic CD22 or CD79a

- *T Lineage:* Surface or cytoplasmic expression of CD3

Any leukemia that cannot be categorized into one of the above three lineages is categorized as belonging to the ambiguous lineage, which includes mixed phenotype acute leukemia (MPAL) and acute undifferentiated leukemia.

5.5.9 Flow Cytometric Analysis of Mature Lymphoid Neoplasms

The WHO classifies mature lymphoid neoplasms by integrating their morphology, immunophenotypes, genetic abnormalities, and clinical features. FCI is an integral part of an investigation of mature lymphoid neoplasms in the diagnosis, classification, prognosis (in few subgroups), and monitoring of treatment response. In non-Hodgkin's lymphoma diagnosis, FC is a more sensitive, specific, and rapid tool when compared to immunohistochemistry. Of note, flow cytometry has high efficacy when evaluating lymphoid neoplasms for antibody-based therapy (such as rituximab, alemtuzumab), as it specifically identifies the surface expression of the targeted antigen.

Mature B-Cell Neoplasms

Mature B-cell neoplasms are a clonal expansion of B cells (expressing either kappa or lambda light chain) and are usually associated with immunoglobulin (Ig) gene rearrangement. In addition to lineage assignment, FCI plays a pivotal role in B-cell non-Hodgkin's lymphoma by determining clonality, i.e., Ig light chain restriction, identifying the size of the cells (large or small), and evaluating aberrant antigen expression. In a normal or reactive B-cell population, the ratio of surface kappa light chain-expressing B cells to surface lambda light chain-expressing B cells is 4:1–1:1 and a deviation from this range alerts the underlying monoclonal B-cell proliferation [42]. Of note, the kappa–lambda ratio may be unable to detect small monoclonal populations whenever admixed with reactive polyclonal B cells and, in such cases, the light chain ratio needs to be evaluated after separation of selective B cells with atypical antigen expression [43]. The absence of surface immunoglobulin (sIg) light chains in mature B-cell proliferation also indicates a mature B-cell neoplasm [43, 44].

Classification

Mature B-cell neoplasms are assigned a lineage based on their expression of one of the lineage-specific markers like CD19 (most specific), CD22, CD79a, CD79b, and CD20. Traditionally, some researchers classified mature B-cell neoplasms based on their expression pattern of CD5 and CD10 into four arbitrary subgroups such as [25]:

1. CD5$^+$, CD10$^-$ [chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), B-cell prolymphocytic leukemia (B-PLL)]
2. CD5$^-$, CD10$^+$ [follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma (BL)]
3. CD5$^-$, CD10$^-$ [marginal zone lymphoma (MZL), DLBCL, lymphoplasmacytic lymphoma (LPL), hairy cell leukemia (HCL)]
4. CD5$^+$, CD10$^+$ (FL, DLBCL, BL)

Once the arbitrary grouping is done, more specific antigens are studied to distinguish each entity from the other in particular subgroups. The majority of cases in CD5$^+$, CD10$^-$ lymphoma subgroups are constituted by CLL and MCL, which can be distinguished by markers like variable CD23, moderate CD200, dim CD20, and dim surface Ig in CLL (see Fig. 1) vs. negative CD23, negative CD200, moderate-to-bright CD20, and moderate surface Ig in MCL [43, 45]. Further confirmation of MCL can be performed by cyclin-D1 studies [46]. Atypical CLL (aCLL), a distinct clinical and immunophenotypic entity, differs from classical CLL by expressing bright CD20 and bright surface Ig [47]. B-PLL is a morphological diagnosis with peripheral blood showing >55–90% prolymphocytes and immunophenotypically expressing bright CD19, bright CD20, bright IgM/IgD, less frequently CD5 and CD23, and dim CD200 [47]. A subset of DLBCL is CD5$^+$ and can be differentiated from small cell CD5$^+$ lymphomas by their morphological size and an associated high FSC [25]. CD5$^+$ MZL lymphomas constitute a small subset, and it is difficult to distinguish from other CD5$^+$ lymphomas [25].

FL is characterized by the expression of dim CD19, CD10, and intracellular bright homogeneous BCL2 expression [48, 49]. DLBCL is a heterogeneous category, with 20–40% of them being CD10$^+$, and can be sometimes distinguished from grade 3 follicular lymphomas by the size of the cells and also the presence of t(14,18) [50, 51]. BL is a high-grade lymphoma with distinctive morphological features like large cells, with bluish cytoplasm, cytoplasmic vacuoles, and characteristic immunophenotypic features like a moderate expression of CD19, CD20, CD38, CD10, CD81, and variable CD86 and the absence of BCL2 and positive expression of BCL6 [51]. Sometimes it is difficult to distinguish from DLBCL by morphology and immunophenotyping, which can be solved by a demonstration of t(8;14).

Hairy cell leukemia (HCL) is another example where FCI plays the foremost role in diagnosis as well as in residual disease monitoring and is characterized by cells showing high FSC and SSC and bright expression of B-cell antigens like CD19, CD20, and CD22 in combination with co-expression of CD11c CD25, CD103, CD123, and CD305 [52, 53]. The HCL variant shows a similar phenotype, except for the characteristic absence of CD25 and CD123 [9]. It is difficult to distinguish LPL from MZL, as the majority of the cases in both entities are CD5C and D10, along with moderate expression of CD19 and CD20. Few features that can help in diagnosing LPL are serum monoclonal M-band in case of LPL, bright immunophenotypic expression of IgM, and demonstration of clonal plasma cells [11].

Mature T- and Natural Killer (NK)-Cell Neoplasms

Mature T- and NK-cell neoplasms are relatively rare when compared with B-lineage non Hodgkin lymphoma (NHL). These neoplasms aberrantly lack one of the following T-cell antigens: CD2, CD3, CD5, and CD7. In most of the cases, there is CD4- or CD8-restricted population ($CD4^+$ is more common). Also demonstrated are $CD8^+$ T-cell lymphomas, $CD4^+$ and $CD8^+$ lymphomas, and double-negative lymphomas [43]. Apart from the aberrant loss of antigens and CD4/CD8 restriction, it is important to establish clonality using T-cell receptor (TCR) Vβ repertoire FC analysis [54]. Mycosis fungoides (MFs), Sezary syndrome (SS), T-cell prolymphocytic leukemia (T-PLL), anaplastic large cell lymphoma (ALCL), adult T-cell leukemia/lymphoma (ATLL), and angioimmunoblastic T-cell lymphoma (AITL) constitute the majority of the $CD4^+$ T-cell neoplasms [43]. T-cell neoplasms can be further classified into these subtypes by clues like frequent loss of CD7, the absence of CD26 and skin lesions in MFs [9], $CD30^+$, ALK^+ large cells, and frequent loss of CD5 in ALCL [43]. Frequent loss of CD7, high levels of CD25, and serological evidence of HTVL favor ATLL [43]. CD10, PD-1, BCL2 and other follicular markers help in the diagnosis of AITL [25]. T-PLL is characterized by a high peripheral blood WBC count (>1 lakh) and T-cell leukemia/lymphoma 1 (TCL1) expression [9, 10].

5.5.10 Flow Cytometric Analysis in Plasma Cell Neoplasms (PCNs)

FCI is widely used in the diagnosis of PCNs, including a precursor condition, monoclonal gammopathies of undetermined significance (MGUS). Plasma cells (PCs) are gated by taking into account the expression of CD38 (bright) and CD138 (bright). Together with CD38 and CD138, normal PCs express dim CD19, bright CD27, dim CD45, and cytoplasmic Ig light chains (kappa and lambda) and are negative for other lymphoid and myeloid antigens [55]. PCs typically show high FSC and relatively high SSC. Neoplastic PCs characteristically show the following immunophenotypic features [55]:

- Loss of normal antigens, e.g., CD19 and CD45
- Decreased expression of antigens, e.g., CD38 and CD27
- Aberrant expression of antigens, e.g., CD56, CD20, CD28, and CD117
- Cytoplasmic Ig light chain restriction, e.g., either kappa or lambda

Novel applications of FCM in plasma cell neoplasms include prognostication, identification of potential therapeutic target antigens, and detection of minimal residual disease (MRD) for monitoring of treatment response [9].

5.5.11 Flow Cytometric Analysis in Myelodysplastic Syndromes (MDS)

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by dysplastic features of erythroid and/or myeloid and/or megakaryocytic lineages with a varying percentage of blast cells. FCI plays a crucial role in MDS diagnosis by detecting maturation asynchrony and aberrant antigen expression on multiple bone marrow lineages (in comparison to normal cells of that particular lineage) [56]. It also analyzes aberrancies on myeloid and lymphoid progenitors and can be utilized to quantify the progenitor percentages. Normal hematopoietic cells show reproducible patterns of antigen expression and synchronous maturational patterns compared to normal, dyspoietic cells in MDS, which show the following:

- Increased or decreased intensity and/or loss of normal antigens
- Asynchronous maturation
- Aberrant expression of antigens (lineage infidelity)

The antigens commonly used for illustration of asynchronous maturation patterns in granulocytes are CD11b, CD13, CD15, CD16, CD33, CD34, CD45, CD117, and HLADR; in monocytes, they are CD13, CD14, CD15, CD33, CD36, CD45, CD64, and HLADR; in erythroid cells, they are CD36, CD71, CD105, and CD235a; and for aberrant antigen detection, they are CD2, CD7, and CD56. Based on the number and types of these immunophenotypic abnormalities in blasts, granulocytes, and monocytes, several scoring systems have been published (flow cytometric scoring system (FCSS) like WELLS score, Ogata score, Red score) [57–59]. The European LeukemiaNet Working Group showed a correlation between higher numbers of immunophenotypic aberrancies and increased risk of progression in MDS [60].

5.5.12 Minimal Residual Disease (MRD) Monitoring by FC

Minimal residual disease refers to an extremely low-level neoplastic cell population that can be detected by sensitive laboratory techniques like flow cytometry (immunological MRD) or polymerase chain reaction (PCR) (molecular MRD) in cases with morphological remission at different time points during treatment like day 15 of induction, post-induction, post-consolidation, or at the end of maintenance. FC analysis of MRD is based on two main principles:

- Deviation from normal maturation (neoplastic cells do not follow normal maturation, which is exhibited by their corresponding normal regenerating precursors)
- Identification of leukemia-associated immunophenotypes (LAIPs), which are not expressed by normal bone marrow (BM) or peripheral blood cells, e.g., lymphoid blasts expressing myeloid antigens, or vice versa, as mentioned under ALL and AML.

It is a strong prognostic indicator, depending on which treatment protocols are decided in cases of ALL [61]. In AML, MRD by FCI has a pivotal role in the response and risk assessment in AML and a means of identifying risk groups in patients with otherwise no prognostic markers (cytogenetically normal AML and the absence of molecular subgroups) [62]. FCI can successfully detect and quantify MRD levels up to 1 leukemic cell in 10^4 normal cells and is widely applied in monitoring not only acute leukemia but also mature lymphoid neoplasms like multiple myeloma (MM), CLL, HCL, etc. [9], and its role in acute leukemia is well-established. Recent studies have proven that high-sensitivity FC-MRD (by simply acquiring a higher number of events, more than four million cells) will improve the sensitivity (1 tumor cell in 10^5–10^6) of FC-based MRD comparable to molecular MRD [63].

5.6 The Role of FCI in the Prognosis of Hematolymphoid Neoplasms

FC also plays an important role in identifying the prognostic markers in many hematolymphoid neoplasms, which are described in Table 3 [64].

Table 3 Immunophenotypic markers useful in prognosis of hematolymphoid neoplasms

Disease entity	Immunophenotypic markers	References
CLL	CD38, ZAP 70, and CD49d	[62]
B-ALL	Absence of CD10, CD15 POS, NG2 predicts *MLL* rearrangement	[10]
B-ALL	CRLF2 expression predicting Ph-like ALL	[24, 25]
T-ALL	ETP-ALL phenotype with negative CD5, CD8, and CD1a	
AML	RAM phenotype with the absence of HLADR, CD38, dim-to-negative CD45, and bright CD56	[36]
AML	CD56 expression in general	[21]

6 Molecular Hemato-Oncology

Molecular diagnostic techniques are now quintessential, as in the current World Health Organization (WHO) classification of hematopoietic and lymphoid neoplasms [1]; several entities have been essentially defined by their molecular abnormalities.

This section discusses the most used molecular diagnostic assays deployed in a state-of-the-art molecular hemato-oncology laboratory. Because molecular testing is most commonly performed in the context of neoplastic disorders, this section follows the outline of the entities incorporated into the WHO classification.

6.1 An Overview of Molecular Diagnostic Techniques

The basic workflow in a molecular laboratory is depicted in Fig. 2. Once a sample is received, the type of nucleic acid to be extracted (DNA or RNA) depends on the test requested. For most of the point mutation analysis, DNA-based panels are used, whereas for detection of fusions, RNA-based assays are employed. Following nucleic acid extraction, RNA is reverse-transcribed to complementary DNA (cDNA) for further processes. The segment of interest is then exponentially amplified (PCR) using gene-specific primers. PCR entails three steps:

1. **Denaturation** of the nucleic acid—(90–95 °C)
2. **Annealing**—primer binding—(40–70 °C)
3. **Extension**—(70–75 °C)

Once the product is amplified, the amplicons can be analyzed using any of the myriad techniques available

- **Gel electrophoresis**: This is the traditional method of post-PCR analysis. This process involves labeling of the DNA fragments with ethidium bromide (intercalating DNA-binding dye). This technique has been largely replaced by capillary electrophoresis and restriction fragment length polymorphism (RFLP).
- **RFLP**: This involves fragmentation of the amplicons by restriction endonuclease enzymes, which act upon specific nucleotide sequences, leading to the detection of a specific pattern on gel.
- **Sanger sequencing**: DNA sequencing determines the precise order of the four bases (A, T, G, and C) in a given

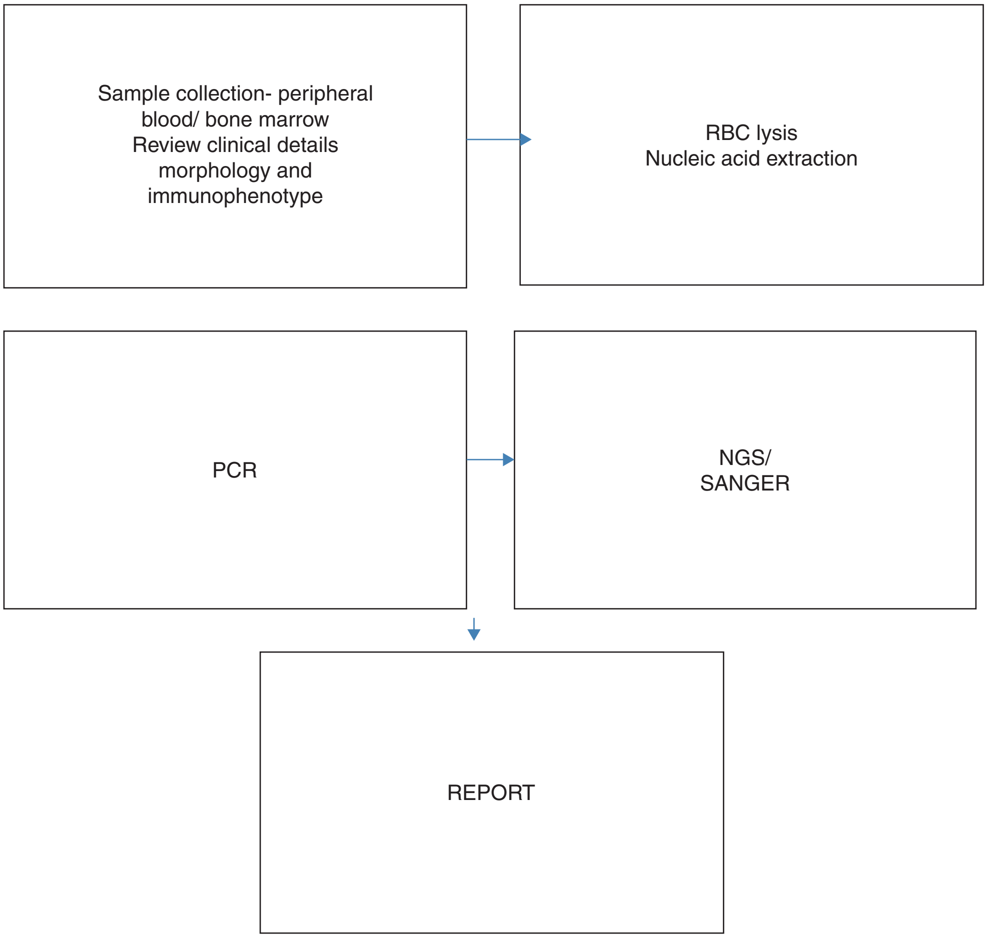
Sample collection- peripheral blood/ bone marrow
Review clinical details
morphology and immunophenotype
RBC lysis
Nucleic acid extraction
PCR
NGS/ SANGER
REPORT

Fig. 2 Basic workflow in a molecular laboratory. Sample collection to the final report

template. Sanger sequencing is the conventional method, which involves DNA synthesis coupled with chain termination. It uses fluorescent-labeled chain terminators, which are modified dideoxynucleotide triphosphates (ddNTPs), in which the 3′-OH group, required for DNA extension, is missing. Thus, labeled fragments of different sizes are obtained, which are then subjected to capillary electrophoresis. The resulting graph is called a chromatogram, which is then aligned with the reference gene to determine the sequence and the variant.

- **Next-generation sequencing (NGS)**: Next-generation sequencing is the more sophisticated technology, which has been developed on the premise of sequencing by synthesis. It involves simultaneous analysis of millions of fragments of DNA, all incorporated within a single test [65, 66]. The library preparation involves complex sequential steps, which finally hybridizes to a two-dimensional flow cell. The bridge-amplification cycle then sets in, culminating in a localized cluster of approximately 2000 similar libraries in a 1-μm diameter. Using sophisticated bioinformatics pipelines, the massive raw data are analyzed to detect the variants. Many platforms are available—Illumina, Roche, and Ion torrent. Similarly, fusions can be looked for by designing primers against the expected fusions or using an anchored multiplex PCR approach, which helps detect novel fusions when one of the partners is known. This technique can also be used to monitor minimal residual disease in acute leukemia during and after treatment.
- **Short tandem repeat (STR)**: STR analysis is the most frequent method for monitoring of donor engraftment after transplant. STRs are polymorphic 2–6 nucleotide tandem repeats that are distributed throughout the genome. Differentiation between individual genomes can be detected owing to the highly polymorphic nature of these STRs. This enables earlier detection of disease relapse, level of donor engraftment, and graft-versus-host disease/graft-versus-tumor effect, thus facilitating therapeutic decisions and interventions. A baseline analysis of both the patient and the donor is necessary to identify informative markers, which can be later used for monitoring of the donor engraftment status [67].
- **Real-time quantitative PCR (RQPCR)**: Real-time PCR monitors the PCR amplification process and detects the amplicons in real time, i.e., when they are produced. In RQPCR, amplification and detection are coupled into a

single step, which helps the detection of amplicons as they are produced. The most common application of this technique in the molecular hematopathology setting is the detection of minimal residual disease (MRD) in patients of chronic myeloid leukemia. The details of the same are discussed under the heading "Chronic Myeloid Leukemia (CML)."

The various assays and their use in the diagnosis of hematolymphoid neoplasms are summarized in Table 4.

6.2 Molecular Diagnosis of Hematolymphoid Neoplasms

6.2.1 Myeloproliferative Neoplasms

Chronic Myeloid Leukemia (CML)

As per the current definition by the WHO, all cases of CML harbor t(9; 22) (q34; q21) and, in approximately 5% cases, other complex or variant translocations involving the *BCR* and *ABL1* genes. The breakpoints in the *BCR* gene on chromosome 22 are heterogeneous and, in most cases, involve exons 13 or 14 of the *BCR* gene, producing a 210-kDa fusion protein (M-bcr). However, in a subset of cases and in few cases of precursor B-cell acute lymphoblastic leukemia, a 190-kDa fusion protein is produced due to breakpoint at exon 1 (u-bcr) [1]. At the diagnostic time point, the identification of the transcript is imperative, to guide future MRD monitoring in these patients. Several techniques are employed for the detection of the fusion:

- **Classical cytogenetics**: Fluorescence in situ hybridization (FISH) is the age-old method that is used to detect the *BCR-ABL1* translocation.
- **Multiplex PCR**: This is the method of choice for transcript identification nowadays and has the advantage of detecting other rare variant transcripts using specific primers. After the initial PCR, the products are electrophoresed on a gel and the specific sizes of the bands guide transcript identification. Rare transcripts detected can be subsequently sequenced for validation [68].
- **RQPCR**: This can also detect the transcripts and quantify the copy number. Baseline copy number detection before initiation of therapy is imperative for future monitoring. Following complete cytogenetic response, RQPCR is

Table 4 Commonly tested molecular abnormalities and methodologies in hemato-oncology

Disorder	Abnormality	Commonly used method for testing
Chronic myeloid leukemia, *BCR-ABL1*-positive	*BCR–ABL1* fusion	RT-PCR
	Molecular monitoring while treatment	RQPCR
	ABL1 kinase domain mutation testing	Sanger sequencing/NGS
Philadelphia-negative myeloproliferative neoplasms	*JAK2 V617F*	RQPCR/ASO-PCR
	CALR	Fragment length analysis
	JAK2 exon 12	Fragment length analysis Sanger sequencing
	MPL W515K/L	Fragment length analysis
Chronic lymphocytic leukemia	*IgH*V mutation analysis	Sanger sequencing
	TP53 mutation analysis	Sanger sequencing/NGS
Acute myeloid leukemia	*FLT3/ITD*	Fragment length analysis
	FLT3/TKD	RFLP
	NPM1	Fragment length analysis/NGS
	CEBPA	Fragment length analysis Sanger sequencing
	c-KIT	Sanger sequencing/ASO-PCR
	Other mutations (*DNMT3A*, *TET2*, *IDH1*, *IDH2*, etc.)	NGS
	Recurrent genetic abnormalities (e.g., *PML-RARA*, *RUNX1-RUNX1T1*, *CBFB-MYH11*, etc.)	RT-PCR
	Monitoring of *PML-RARA*	RQPCR
MDS	*SF3B1*	Sanger sequencing/NGS
	Other mutations (*DNMT3A*, *TET2*, *IDH1*, *IDH2*, etc.)	NGS
Acute lymphoblastic leukemia (ALL)	Recurrent genetic abnormalities	RT-PCR
	BCR-ABL1-like ALL	NGS or MLPA + RQPCR + Sanger sequencing
Hairy cell leukemia	*BRAF V600E*	ASO-PCR
Lymphoplasmacytic lymphoma	*MYD88 L265P*	ASO-PCR
Chimerism testing	STRs	Multiplex PCR + fragment length analysis
Clonality	Ig and TCR gene rearrangement	Multiplex PCR + fragment length analysis

PCR polymerase chain reaction, *RT* reverse transcriptase, *RQ* real-time quantitative, *ASO* allele-specific oligonucleotide, *NGS* next-generation sequencing, *RFLP* restriction fragment length polymorphism, *Ig* immunoglobin, *TCR* T-cell receptor

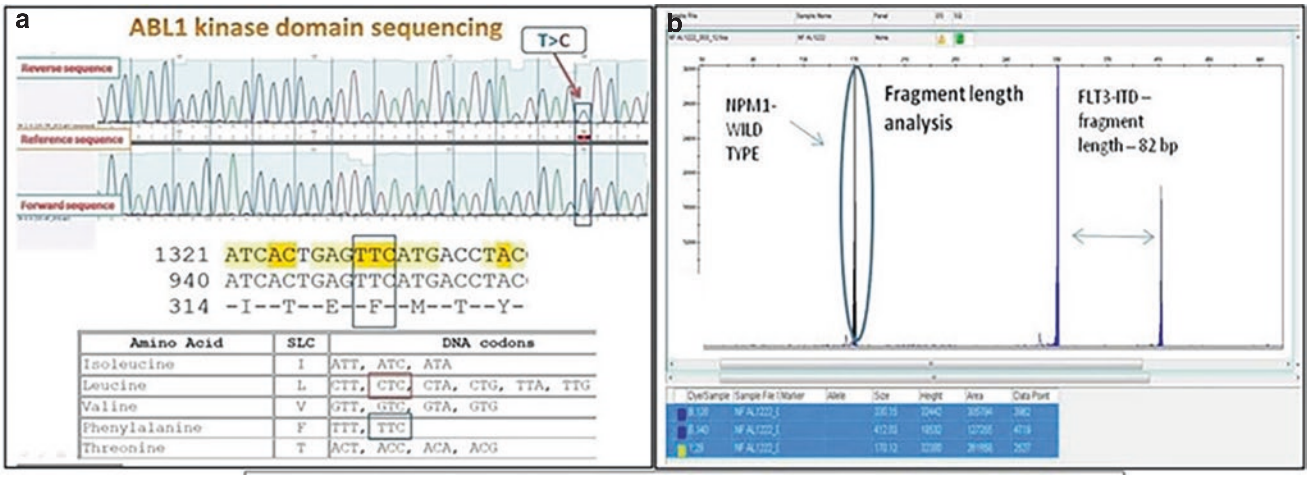

Fig. 3 (**a**) Determination of mutation by bidirectional Sanger sequencing. Here, the bases in TTC (which encode for phenylanaline) is replaced by CTC (encoding for leucine) and hence amino acid phenylalanine (F) is changed to leucine (L) at 317 positions. (**b**) Fragment length analysis to depict *NPM1* and *FLT3-ITD* mutation. Here, *NPM1* (black peak-encircled) is wild-type. There is no mutation in exon 12. *FLT3* (blue peak) shows an internal tandem duplication with a fragment length of 82 bp. The allelic ratio can be calculated by dividing the area of the mutant peak by the area of the wild-type peak

advocated and a major molecular response is defined as a 3-log reduction in the number of *BCR-ABL1* transcripts from the pretreatment baseline [4, 69, 70]. Likewise, although the transient positivity or persistent low-level copy numbers are not predictive of impending relapse, a 1-log change in the level is generally considered significant. Therefore, a rising quantitative PCR result offers the possibility of an early intervention.

- **Kinase domain mutation status**: Imatinib, which is the drug of choice for these patients, acts at the kinase domain in the *ABL1* gene. During the course of therapy, acquired point mutations in this kinase domain may lead to imatinib resistance and hence treatment failure. These mutations are diverse, however the T315I mutation is notable amongst them as it imparts resistance to the second generation tyrosine kinase inhibitors [68, 71]. These mutations can be detected by direct sequencing of the fusion gene, traditionally by Sanger's method, or nowadays using NGS. Other methods that can be employed are allele-specific PCR, pyrosequencing, etc. Figure 3a shows the interpretation of a kinase domain mutation using Sanger sequencing.

Philadelphia-Negative Myeloproliferative Neoplasms

Unlike CML, these are not described by a single recurring molecular abnormality. They include primary myelofibrosis (PMF), essential thrombocythemia (ET), and polycythemia vera (PV). The *JAK2 V617F* mutation is identified in >95% cases of PV and 50–60% of PMF and ET, *JAK2* exon 12 mutations in 3% cases of PV, *CALR* (calreticulin) mutations in 30% of PMF and ET, and *MPL* mutations are seen in 8% of PMF and 3% of ET [1]. The most common *CALR* mutation notated are 5-bp insertion and a 52-base pair deletion. Likewise, the common mutations encountered in the *MPL* gene are *W515L* and *W515K*.

The *JAK2 V617F* mutation can be detected using allele-specific oligonucleotide-PCR (ASO-PCR) [72], or RQPCR can be employed to detect low-level mutations, which may be missed by other methods, including NGS. *MPL* and *JAK2* exon 12 mutations can be detected using ASO-PCR, whereas *CALR* mutations can be detected by PCR followed by fragment length analysis [73, 74].

Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPNs)

Recently, whole-genome sequencing has helped identify recurrent mutations in MDS/MPNs, and these have now been incorporated in the diagnostic criteria, for example, *TET2*, *SRSF2*, *ASXL1*, and *SETBP1* mutations in chronic myelomonocytic leukemia, *SETBP1* and *ETNK1* mutations in atypical CML, *PTPN11*, *KRAS*, *NRAS*, *NF1*, and *CBL* mutations in juvenile myelomonocytic leukemia, and *JAK2 V617F*, *CALR*, *MPL*, and *SF3B1* mutations in MDS/MPNs with ringed sideroblasts and thrombocytosis [1].

6.2.2 Myelodysplastic Syndromes

The *SF3B1* mutation is the sole genetic abnormality that is a part of the diagnostic criteria for myelodysplastic syndrome (MDS) with ring sideroblasts. Patients with *TET2* and *DNMT3A* mutations respond well to hypomethylating agents and those with MDS with 5q deletion having the *TP53* mutation respond less well to lenalidomide [1, 75].

Table 5 Myeloid neoplasms with germline predisposition

Myeloid neoplasms with germline predisposition (MNGP)	MNGP without a preexisting disorder or organ dysfunction • AML with germline *CEBPA* mutation • MN with germline *DDX41* mutation MNGP and preexisting platelet disorders • MN with germline *RUNX1* mutation • MN with germline *ANKRD26* mutation • MN with germline *ETV6* mutation MNGP and other organ dysfunctions • MN with germline *GATA2* mutation • MN associated with BM failure syndrome • MN associated with telomere biology disorders • JMML associated with neurofibromatosis, Noonan syndrome, or Noonan syndrome-like disorders • MN associated with Down syndrome

AML acute myeloid leukemia, *MN* myeloid neoplasm, *BM* bone marrow, *JMML* juvenile myelomonocytic leukemia

6.2.3 Myeloid Neoplasms with Eosinophilia and Gene Rearrangements

This category in the WHO includes four distinct entities defined by specific gene rearrangements. These are *PDGFRA*, *PDGFRB*, *FGFR1*, and one with a *PCM1–JAK2* fusion. These can be detected using reverse-transcription-PCR (RT-PCR) or FISH [1].

6.2.4 Myeloid Neoplasms with Germline Predisposition

These are AML or MDS patients with a germline mutation and exhibit distinctive clinical and genetic abnormalities. Table 5 depicts the various entities included under this category. It is important to consider these entities in the setting of high mutant allele burden in a patient with defined clinical features. Germline testing is recommended using DNA from skin fibroblasts [1, 76].

6.2.5 Acute Myeloid Leukemia

According to WHO, seven distinct clinicopathological entities are defined by the presence of specific recurring molecular abnormalities: *RUNX1-RUNX1T1*, *CBFB-MYH11*, *PML-RARA*, *MLL* rearrangement, *DEK-NUP214*, *BCR-ABL1*, and *RBM15-MKL1*. These can be detected by RNA sequencing. Other molecular abnormalities described in AML, which have therapeutic and prognostic implications, include *NPM1*, *FLT3* (*TKD* and *ITD* mutations), *CEBPA*, *c-KIT*, *RUNX1*, and, commonly, *IDH1* and *IDH2*. Next-generation sequencing assays utilizing single-molecule molecular inversion probes are used for the detection of these mutations. *FLT3-ITD* and *NPM1* can additionally be detected using fragment length analysis, as depicted in Fig. 3b *PML-RARA* can be monitored using RQPCR [77, 78].

6.2.6 Clonality Assays in Lymphoproliferative Disorders

Tests for monoclonal rearrangements of the immunoglobulin (Ig) and the T-cell receptor (TCR) loci are commonly performed assays [1]. The results of these assays should be cautiously interpreted in the context of the clinical and morphological findings, excluding the potential false positives and false negatives. These can be detected using PCR followed by capillary electrophoresis.

6.2.7 Precursor B-Cell Acute Lymphoblastic Leukemia/Lymphoma (BCP-ALL)

The RT-PCR approach can be employed to detect few of the recurrent genetic abnormalities, which are found commonly in BCP-ALL. Additionally, for the WHO-defined entities, RNA-based NGS assays, as described earlier in AML, can also be used—*BCR-ABL1*, *TEL-RUNX1*, *MLL* rearrangement, and *GATA2-MECOM*. A new entity incorporated in the recent WHO edition is Philadelphia-like ALL, which can harbor rare fusions that can be detected by the same NGS approach [1, 79].

6.2.8 Precursor T-Cell Acute Lymphoblastic Leukemia/Lymphoma (T-ALL)

Recurrent cytogenetic abnormalities have been described in T-ALL cases; however, a risk-stratified treatment strategy based on molecular abnormalities has not yet been devised; hence, molecular studies for the identification of these abnormalities are rarely performed in routine practice.

6.2.9 B-Cell Lymphoproliferative Disorders

Chronic Lymphocytic Leukemia

Studies have shown that the mutational status of the *IGH* locus carries prognostic significance in CLL. During normal B-cell maturation and activation, the *IGH* locus undergoes somatic hypermutation in the germinal center. By sequencing the portions of the clonally rearranged *IGH*, the mutational status of the neoplastic cells may be determined. The mutated genotype has been associated with a favorable outcome compared to the unmutated genotype [80].

Because patients carrying *TP53* abnormalities are resistant to chemoimmunotherapy, *TP53* mutation analysis should always be performed before initiation of treatment [81].

Hairy Cell Leukemia

Hairy cell leukemia harbors the characteristic *BRAF V600E* mutation, for which targeted therapy (vemurafenib) is available. This can be detected using allele-specific PCR or direct sequencing by any of the methods [82].

Lymphoplasmacytic Lymphoma

MYD88 L265P is a recurring mutation in patients with Waldenström macroglobulinemia that can be helpful in differentiating it from non-IgM LPL and B-cell non-Hodgkin's lymphoma that have similar features [83]. Extremely sensitive and specific ASO-PCR assays have potential benefit in diagnosis and in the assessment of response [84].

6.2.10 T-Cell Lymphoproliferative Disorders

In most cases, the diagnosis of these is rendered on the basis of morphological and phenotypic findings. Clonality studies are useful to confirm the presence of the monoclonal T-cell population. Approximately 60–80% cases of anaplastic large cell lymphoma harbor a translocation involving the *ALK* gene at 2p23. These are best detected using break-apart probes by FISH. However, routinely, immunohistochemistry is used to demonstrate this [1].

6.2.11 Plasma Cell Neoplasms

Cytogenetic abnormalities are present in almost all cases of myeloma, and a subset of these has prognostic implications. The most frequent translocations involve the *IGH* locus [1]. Seven recurrent oncogenes are involved in this translocation: *CCND1*, *MAF*, *FGFR3/MMSET*, *MAFB*, *MAFA*, *CCND2*, and *CCND3*. Mutations in *TP53* and genes in the nuclear factor kappa B (NF-kβ) pathway are associated with tumor progression. These can be detected using direct sequencing of bone marrow samples. Some tumor subclones have RAS pathway mutations, which are important as a specific therapeutic regimen may target one or more specific subclones but have little or no effect on other subclones [1].

Take-Home Points

- Molecular diagnostics is an integral component in the diagnosis of a hematolymphoid malignancy.
- WHO-defined entities necessitate the demonstration of specific molecular abnormalities.
- Molecular diagnosis guides therapeutic regimen and has prognostic implications in many of these entities.
- It therefore remains important that pathologists evaluating peripheral blood, bone marrow, and lymphoid tissue samples continue to be familiar with the spectrum of available molecular diagnostic techniques and be able to integrate their results with the findings of other ancillary studies.

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Microbiology in Oncology

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Abbreviations

BAL	Bronchoalveolar lavage
CLSI	Clinical and Laboratory Standards Institute
CNS	Central nervous system
EUCAST	European Committee on Antimicrobial Susceptibility Testing
HP	Histopathology
HSCT	Hematopoietic stem cell transplantation
MALDI-TOF	Matrix-assisted laser desorption/ionization time of flight
MS	Mass spectrometry
NDBAL	Non-direct bronchoalveolar lavage
NGS	Next-generation sequencing
PCR	Polymerase chain reaction
WGS	Whole-genome sequencing

1 Introduction

Infections are an important cause of morbidity and mortality in patients with neoplastic diseases. Infections may either coexist with malignancies posing diagnostic difficulties or may be complications of a treatment. The introduction of aggressive chemotherapeutic regimens, resulting in prolonged and profound neutropenia, promotes invasion by microorganisms. Most often, these infections are of a bacterial etiology. There are several factors like the primary disease, the degree of immunosuppression, the chemotherapeutic regimens used, hematopoietic stem cell transplantation (HSCT), etc. that predispose to certain patterns of infections. For example, candidemia is important in patients with prolonged neutropenia and mucosal damage. Infections with filamentous fungi like Aspergillus, develop in patients with prolonged and profound neutropenia. Herpes simplex infection may be reactivated in immunosuppressed patients with leukemia.

The current need is to provide accurate, rapid diagnosis of these infections and further guide clinicians on the management and prognosis. The clinical microbiologist and the microbiology laboratory both play a vital role in the management of neoplastic diseases. This highlights the need for a strong partnership between the treating clinician and the clinical microbiologist.

The initial evaluation requires three questions to be answered

1. Is the etiology of the illness microbial?
2. What is the identity of the microorganism?
3. What is the susceptibility profile of the microorganism?

The timely selection of an appropriate diagnostic test has a significant impact on the survival of patients.

Newer methodologies are more sensitive with a rapid turnaround time, but there are several challenges in the interpretation of results.

The current era of diagnostics is aided by several advances, including surrogate markers and molecular tools. The philosophy should be to integrate new technologies with conventional microbiology for the successful and accurate identification of microorganisms encountered in the laboratory.

2 Specimen Selection, Collection, and Processing

The quality of the results and their interpretation is entirely dependent on the choice and quality of specimens submitted to the laboratory for analysis. Health-care personnel collecting specimens should be aware of this and follow standard

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protocols for collection and optimize the time of transportation to the laboratory.

There are three stages for laboratory tests

1. Preanalytical stage: This involves selection of the test, type of specimen to be collected for analysis, labeling, and transportation to the laboratory.
2. Analytical stage: The specimen sent is analyzed by the laboratory for the presence of specific microorganisms. The clinical microbiologist then interprets the results, in the context of the case, differentiating commensals, contaminants, and pathogens.
3. Postanalytical stage: The laboratory results are used by the treating clinician to determine the therapy, if any, to the patient.

The preanalytical stage is the most important stage in laboratory testing. If the wrong test is ordered, or the wrong specimen is collected, wrongly labeled, or improperly transported, then the results are affected and the treatment administered will be inappropriate.

The importance of specimen collection is often underestimated. There are several causes of fever with chills, and only a careful history and physical examination will result in the selection of an appropriate specimen. Both the method of specimen collection and the rapid transportation to the laboratory for testing are equally important. Some pathogenic microorganisms lose their viability and may not be recovered if the specimens are not appropriately transported and/or stored. Therefore, rapid transport of specimens is important for optimal accuracy of analytical results.

2.1 Direct Examination

Gross or macroscopic examination: Once a specimen is received in the laboratory, the first step is to evaluate its gross appearance. This often indicates the likely cause of infection. Infected specimens, namely, urine and cerebrospinal fluid, often appear cloudy due to the presence of white blood cells and microorganisms. Stools specimens may show worms like *Ascaris lumbricoides*. Pus samples from a cold abscess have a typical cheesy appearance. Infected specimens from the lower respiratory tract appear as “purulent” sputum specimens. The presence of visible blood should be noted.

Microscopic examination: This is rapid, easy-to-perform, inexpensive, and available round the clock. It is not as sensitive or specific as culture or some molecular tests but is useful in certain situations for a rapid diagnosis.

Wet mounts: The specimen is mixed with normal saline and viewed directly under a microscope. This tool is useful for the examination of genital secretions for parasites like *Trichomonas vaginalis* and the presence of yeast cells. Modifications with potassium hydroxide (10% KOH) are useful for the visualization of fungal mycelia from skin scrapings. The addition of India ink is used for the visualization of Cryptococcus and Calcofluor white, and a fluorescent stain can be used for the direct visualization of fungal mycelia in tissue specimens. Stool specimens can be screened for ova and cysts by direct examination with saline and 5% Lugol’s iodine.

Gram stain: This is the most frequently used stain in microbiology and serves as a rapid and easy-to-perform diagnostic tool. It differentiates bacteria based on their staining characteristics into Gram-positive (violet) and Gram-negative (pink) and based on their morphology into cocci or bacilli. This basic stain can be used directly on specimens like pus and sputum as an indicator of the type of infection. A pus sample showing Gram-positive cocci in clusters is an indication that this infection is caused by *Staphylococcus aureus*. A sputum sample with plenty of pus cells and Gram-positive diplococci, both intracellular and extracellular, indicates this pneumonia to be caused by *Streptococcus pneumonia*.

Staining of acid-fast organisms: Mycobacteria have a thick outer coat of mycolic acid, which is refractory to dyes like Gram stain. Stains like carbol fuchsin or auramine–rhodamine can form complexes with mycolic acid. These complexes are not washed out by acid alcohol. This characteristic is used for the identification of *Mycobacterium tuberculosis* in sputum and other specimens. Furthermore, modifications of this are used to identify organisms like *Nocardia* in specimens or from cultures and *Cryptosporidium parvum* with a special modification called the Kinyoun cold stain.

Direct fluorescent antibody stains: This is a rapid tool for the detection of viral antigens on infected cells from nasopharyngeal swabs for respiratory syncytial virus, Legionella infections, etc. This is frequently used for the detection of organisms that cannot be easily cultured (Figs. 1 and 2).

Diagnosis of agents from peripheral blood and tissue sections: Peripheral blood is the specimen of choice for the detection of Plasmodia, Babesia, trypanosomes, and microfilaria. Stained tissue sections can be used for the diagnosis of mycelial fungi, yeasts, Histoplasma, and *Sporothrix schenkii*. Parasites can also be visualized directly in sections like *Trichinella spiralis* and larvae and adult forms of parasites.

Antigen detection: A variety of tests are available for the detection of specific antigens of bacteria, viruses, fungi, and parasites. The test formats are either enzyme immunoassays or latex agglutination. Cryptococcus latex agglutination is a commonly used test in practice. Galactomannan assays and beta-D-glucan assays are enzyme immunoassays for the

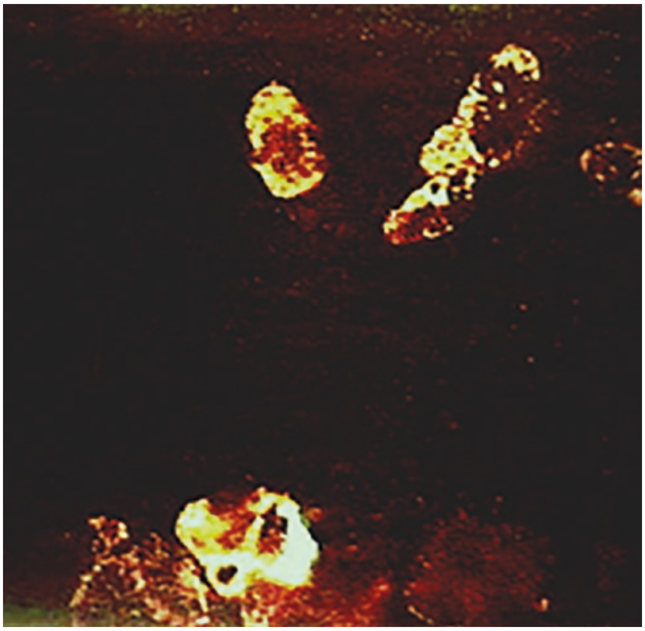


Fig. 1 RSV antigens in nasopharyngeal swabs

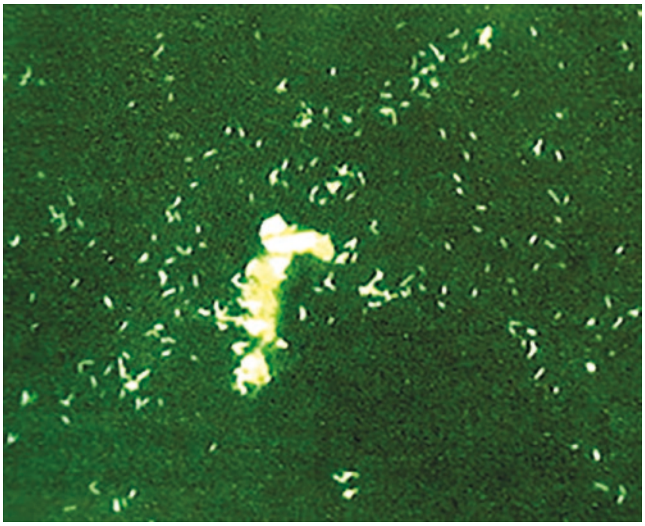


Fig. 2 *Legionella pneumophilia* by immunofluorescence

galactomannan antigen of Aspergillus and other fungi including *Pneumocystis jirovecii*, respectively.

2.2 Molecular Diagnostics

Molecular methods are now routinely incorporated into clinical microbiology, with a shift from conventional methods of microscopy and culture to rapid methods like antigen detection. However, clinicians need to be updated on available methods and, more importantly, on interpretation in the clinical context and the pitfalls.

A combination of classical techniques and new technologies is vital for the successful, accurate identification of all microorganisms encountered in the laboratory.

Polymerase chain reaction (PCR): PCR is best used when conventional clinical microbiological diagnostic procedures are inadequate, time-consuming, difficult, or when the organisms cannot be cultured. This functions as a molecular fingerprint to help identify microbes. Nested PCR increases the sensitivity and specificity of the conventional PCR. This tool has the greatest impact on clinical virology due to its increased sensitivity, specificity, and reduced turnaround time. This eliminates the time-consuming tasks of maintaining cell lines, immunostaining, and viral cultures. The test results assist in the early recognition of infections, directing and monitoring antiviral therapy.

Technological advances in automation from manual in-house to commercial Food and Drug Administration/in vitro diagnostic (FDA/IVD)-approved systems and the introduction of real-time PCR for quantitation and digital PCR has resulted in better utilization of this tool. Quantitation is essential for disease progression, prognosis, and response to antivirals for monitoring infections like human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein–Barr (EBV), human herpes virus 6 (HHV6), and BK virus infections.

Sanger sequencing: The original method described in 1976 has the limitation of a single amplicon and has undergone modifications. Sequencing is used in diagnostic microbiology for the identification of microorganisms, detection of resistance mechanisms like extended spectrum beta lactamases (ESBL) and Methicillin resistant *Staphylococcus aureus* (MRSA), and detection of drug resistance.

Automation allows the reaction to be performed in a single tube with different fluorochromes for each base, and the resulting electropherogram is matched with the reference sequences of standard databases for identification.

Next-generation sequencing (NGS) and whole-genome sequencing (WGS): These are high-throughput methods that encompass several different technologies at a low cost.

NGS with amplicon sequencing is valuable for the prediction of oncogenic potential or antimicrobial resistance. It is useful for the identification of Mycobacteria and the prediction of resistance to anti-tubercular drugs, viz., rifampicin, isoniazid (INH), pyrazinamide, and ethambutol. Pyrosequencing is useful for epidemiological infections during outbreaks.

Mass spectrometry (MS): Matrix-assisted laser desorption/ionization time-of-flight MS (MALDI-TOF-MS) has been recently introduced to clinical laboratories for the identification of bacteria, Mycobacteria, including nontuberculous

Mycobacteria, yeasts, and fungi. This test requires growth of the organism and is low-cost, rapid, and takes about an hour for the results. It is used for the direct identification of organisms in positive blood cultures and urine specimens. There are ongoing studies for antimicrobial susceptibility testing.

Syndromic panel-based testing: A recent development has been the introduction of syndromic panels for testing in clinical microbiology laboratories. Commercial panels for the rapid detection of pathogens in positive blood cultures, respiratory specimens, gastrointestinal (GI) specimens, and central nervous system (CNS) infections are now available. These are multiplex tests that enable rapid diagnosis, allowing the timely management of infections. However, they require a thorough evaluation for clinical practice, proper selection, utilization, and interpretation.

Rapid testing of positive blood cultures: This is a multiplex PCR that detects organisms and resistance genes from positive blood culture bottles in 1–3 h. The disadvantages of this system are that there are fixed panels that do not cover all microorganisms and false-positive results are known. Hence, these are currently being used as "add-on" tests to conventional methods of blood culture.

Multiplex detection of respiratory pathogens: There are several FDA-approved multiplex panels that detect a range of viruses, including adenoviruses, coronaviruses, influenza viruses, parainfluenza viruses, and respiratory syncytial virus and bacteria like *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*.

These tests are currently under evaluation for their clinical and economic impact. The major limitations are fixed panel tests, reduced sensitivity for some agents, inability to differentiate between colonization and infection, and possible missing of co-infections. The use of nasopharyngeal swabs as specimens for testing may result in missing lower respiratory tract infections, necessitating further procedures for the collection of bronchoalveolar lavages (BALs).

Prolonged shedding of some respiratory agents in immunocompromised patients requires interpretation in the clinical context.

Multiplex detection of GI pathogens: Panels that cover pathogens for diarrheal illnesses include bacteria like Campylobacter, Salmonella, Shigella, Vibrio, Yersinia, and *Escherichia coli*, viruses like norovirus, rotavirus, astrovirus, adenoviruses, and sapovirus, and parasites like Cryptosporidium, *Entamoeba histolytica*, and *Giardia lamblia*. This panel is of public health importance, and the ideal panel for testing is still unknown.

Multiplex testing for CNS infections: Panels include CMV, enterovirus, HSV 1 and 2, HHV6, and varicella zoster virus (VZV), bacteria including *E.coli*, *Haemophilus influenza*, Listeria, Neisseria, Streptococci, and Cryptococcus. The results of testing are available is less than 1 hour. This has been a recent introduction, and the results of evaluation studies are not available.

Molecular tests have been incorporated into routine diagnostics in oncology in the following areas

- Cytomegalovirus DNA testing is conducted weekly for patients undergoing bone marrow transplantation. This is performed by real-time PCR, for monitoring treatment with antivirals.
- Testing for hepatitis B infections for monitoring viral loads during therapy is now a routine practice. The technology is real-time quantitative PCR.
- Hepatitis C virus (HCV) infections are confirmed following a screen test with a positive result by reverse transcription-PCR (RT-PCR). Quantitation is carried out in HCV infections to determine the duration of antiviral treatment.
- Human papilloma virus (HPV) testing is used as a screening tool for the high-risk genotypes for cervical cancer. Several test systems are available, including E6 and E7 oncoprotein detection. The DNA by hybrid capture for screening 15 high-risk HPV types is an approved test. Real-time PCR and chip-based tests are also available for screening and genotyping.
- HIV RT-PCR is performed for HIV diagnostics and for monitoring viral loads during treatment of HIV infections.
- GeneXpert is a fully automated system that is used for the detection of *Mycobacterium tuberculosis* and rifampicin resistance in pulmonary and extrapulmonary samples. This is a rapid test that produces results within 2 hours.

Molecular diagnostics is a powerful tool; the results allow timely diagnosis and influence management decisions and treatment, but there are several unanswered questions listed below:

- What is the duration of DNA persistence after treatment?
- Does DNA persist even after eradication of microbes?
- What are the blood DNA levels after microbial lysis?
- Is bacterial RNA a better indicator of the current infection?
- How can PCR distinguish between colonization, latent infection, active infection, and relapsing infection?

In conclusion, there is a need for careful integration of what is technically feasible with what is clinically important because clinical microbiology is an "interpretative science."

2.3 General Guidelines for Specimen Processing for Bacterial and Fungal Culture

The specimens commonly sent for culture are blood, pus, respiratory tract secretions, urine, fecal specimens, cerebrospinal fluid, sterile body fluids like pleural fluid, ascitic fluid pericardial fluid, drain fluids, tissues, and biopsies sometimes collected under computed tomography (CT) or ultrasonogram (USG) guidance and catheters from intravascular sites. In some cases, specimens are processed quantitatively, for example, catheter tips are processed by the Maki's method, by rolling them three times on a culture plate. Urine and non-direct bronchoalveolar lavage (NDBAL) samples are also processed quantitatively. Specimens for mycobacterial and fungal culture need to be processed in special media, and the laboratory requires intimation to that effect. There are written guidelines for specimen collection, transportation, and rejection of inappropriately collected specimens. Specimens that are collected after hours should be sent in transport media. Oncology centers have some unique requirements and requests, which require discussion with the laboratory physician.

Culture: Culture is the commonly used technique for the detection of bacteria. The majority of human pathogens grow in 1–2 days of incubation. Mycobacteria are slow-growing and take nearly 3–4 weeks for the detection of growth. Mycelial fungi take at least 48 hours for visible growth. Longer incubation periods of 3 weeks are required for dimorphic fungi like Histoplasma. Some microorganisms are fastidious (organisms with highly complex growth requirements) and have special requirements like *Neisseria meningitis*, which requires carbon dioxide for optimum growth, and *Haemophilus influenza* and *Helicobacter pylori*, which require microaerophilic conditions for growth. Anaerobes require special collection systems, transportation, media, and growth conditions. Tissue samples need to be homogenized for processing. In patients with suspected zygomycosis, the tissues need to be carefully processed as this delicate fungus gets killed during processing. Appropriate processing of samples and recovery of etiological agents depend on the clinical details provided. This also decides the media used for processing. There are different media and growth conditions for bacteria, fastidious microorganisms, anaerobic bacteria, and fungi, including dimorphic fungi. The majority of microorganisms grow best at 37 °C; however, some clinically significant organisms require low temperatures (4 °C), whereas some grow at higher temperatures (42 °C). Some skin pathogens like dermatophytes grow better at 30 °C. Incubation temperatures therefore need to be modified depending on the suspected infection.

Media: The selection of media is dependent on the organisms to be isolated. Microorganisms have different nutritional requirements. The basic medium used for Gram-positive organisms is sheep blood agar. This allows the visualization of hemolysis, which differentiates Streptococci, Staphylococci, etc. The enrichment with blood allows the growth of many fastidious organisms. This is heated to chocolate agar for the growth of Neisseria and, when supplemented with growth factors, is used to isolate *Haemophilus influenzae*. Most Gram-negative rods grow on MacConkey agar, which is a selective medium with crystal violet and bile salts that inhibit some Gram-positives. Special isolation media are required for organisms like Legionella and Bordetella, whereas the recovery of stool pathogens like Shigella and Salmonella requires selective media (Figs. 3 and 4).

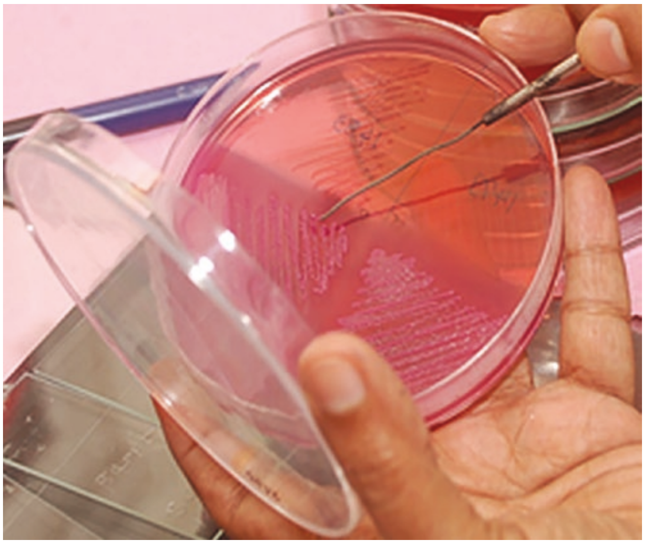


Fig. 3 Growth in MacConkey's medium

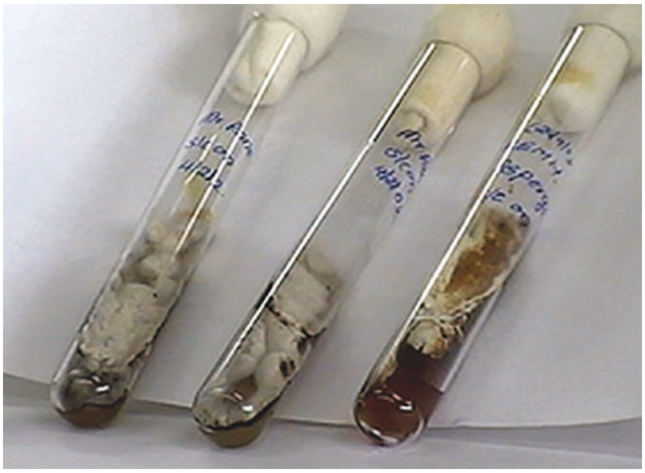


Fig. 4 Growth of mycelial fungi

Mycobacterial cultures are performed after decontamination of specimens in a Lowenstein–Jensen medium and in liquid culture systems (Fig. 5). There are several commercial systems available for the detection and identification of *Mycobacterium tuberculosis.* Most laboratories use molecular tools for the detection of Mycobacteria. In India, many centers still use manual methods for detection.

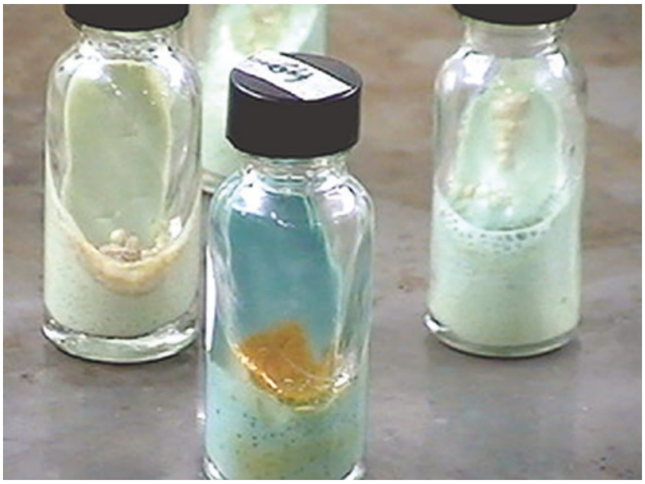


Fig. 5 Growth of Mycobacteria in a Lowenstein–Jensen medium

3 Detection and Identification Methods

Organisms are isolated as growth of colonies on agar plates. These can be identified as pathogens once their significance is established, and they are differentiated from the resident microbiota and colonizers. The appearance of colonies often indicates the identity of an organism. Growth on blood agar with different types of hemolyses is used to identify Streptococci and Staphylococci. Streptococci are further identified based on their susceptibility to differentiation discs of optochin and bacitracin. Optochin-susceptible alpha-hemolytic organisms are presumptively identified as *Streptococcus pneumonia.* The growth of *Pseudomonas aeruginosa* is identified by the green pigment and non-lactose fermenting colonies. Flow charts are available for the identification of bacteria and yeasts based on colony morphology, staining characteristics, motility, pigment production, etc. The identification is confirmed by biochemical tests. Some organisms like the Salmonella species are confirmed by serology and agglutination with specific antisera. Manual biochemical identifications are the gold standard.

Manual identification of yeasts follows a flow chart based on colony characteristics and basic tests like germ tube and urease. The identification is based on carbohydrate assimilation and fermentation reactions, which are matched with standard classifications like the Ahearn's classification.

Identification of mycelial fungi is based on growth characteristics, pigment production and its characteristics, followed by slide culture to determine the pattern of sporulation, which identifies the fungus.

Dimorphic fungi like *Histoplasma capsulatum* are detected in tissues and blood in the yeast form. When they are cultured at 30 °C, they grow in the mycelial form. Confirmation of the identity is possible only after they are converted from the yeast to the mycelial phase in blood-containing media, incubated at 37 °C. It takes several weeks of serial subculture for this conversion from the mycelial to yeast form.

Identification of microorganisms at the species level is important because it helps determine the role that an organism may play in the patient's disease process and influences clinical management.

There are several automated systems available for identification of bacteria and yeasts. Their major disadvantage is they do not take into account morphological characteristics like pigment production, colony morphology, motility, etc. Molecular methods for identification, including MALDI-TOF-MS, have already been discussed.

Molecular epidemiological tools are used for typing organisms during outbreaks.

4 Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing is performed on rapidly growing bacteria once the role of the organism in the disease process is established. There are several methods for testing. The commonly used method is the Kirby–Bauer disc diffusion method (Fig. 6). The results of this accurately predict resistance to antimicrobials. If an antimicrobial is reported as susceptible, then it indicates a likelihood of response to that antimicrobial. Standard interpretative guidelines are used to determine and interpret the results of testing. These may be from the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Fastidious organisms require Mueller Hinton with a blood supplement for the susceptibility testing.

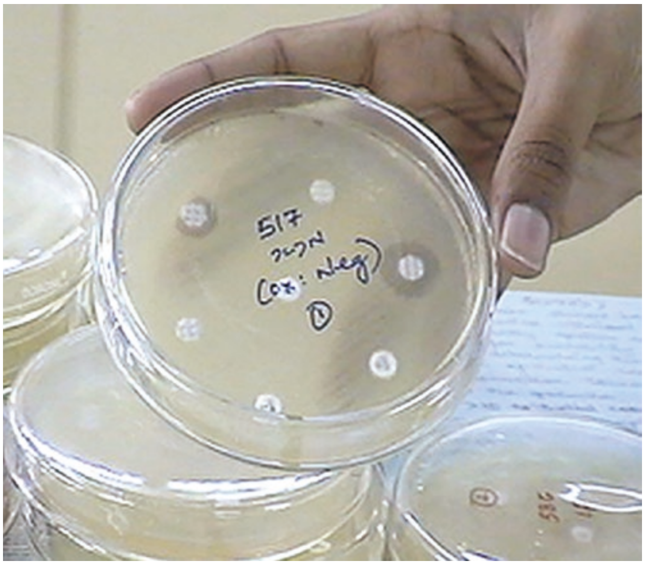


Fig. 6 Kirby–Bauer disc diffusion method

Automated systems that determine the minimum inhibitory concentration of the antimicrobials are increasingly being used in clinical practice. A popularly used method for minimum inhibitory concentration (MIC) testing is the "E" test, a plastic strip that contains a gradient of the antimicrobial (Fig. 7). This strip is applied to a lawn culture of the organism on an agar plate. The point where the zone of inhibition intersects with the strip is the MIC of the antimicrobial tested for the organism.

Micro-broth dilution methods are the standard for many antimicrobials and for antifungal susceptibility testing of yeasts and molds (Fig. 8). Antifungal susceptibility testing methods are now the standard, and interpretative criteria for many antifungals are available. Automated systems like Vitek 2™, Phoenix™, etc. have provision for antifungal susceptibility testing of yeasts. A commercial system called Sensititre™ can be used for antifungal susceptibility testing of molds. In clinical practice, MIC values are used for decisions on the choice of antimicrobials and have become a part of the reporting practice in clinical microbiology.

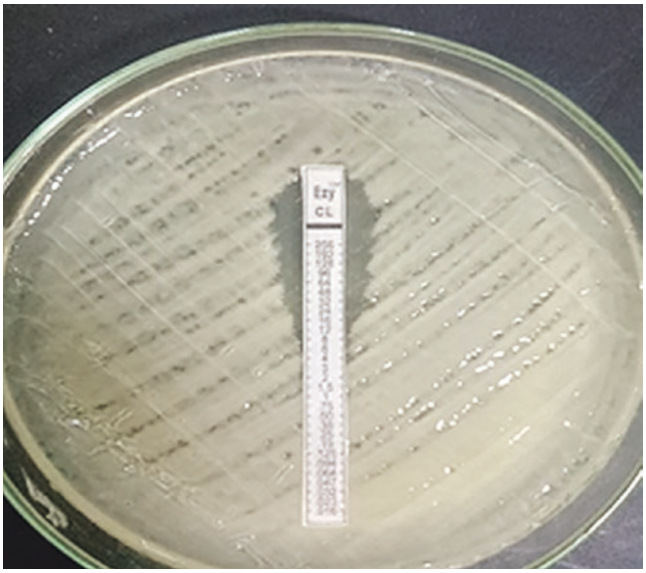


Fig. 7 An "E" test

Susceptibility testing for *Mycobacterium tuberculosis* can be performed in automated systems or manually by the absolute concentration or resistance ratio methods (Fig. 9). Basic laboratories do not perform identification or susceptibility testing of Mycobacteria. Methods are available for the susceptibility testing of nontuberculous Mycobacteria.

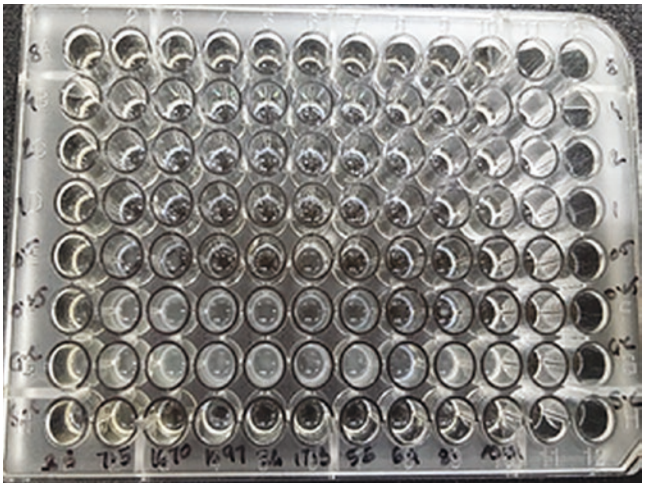
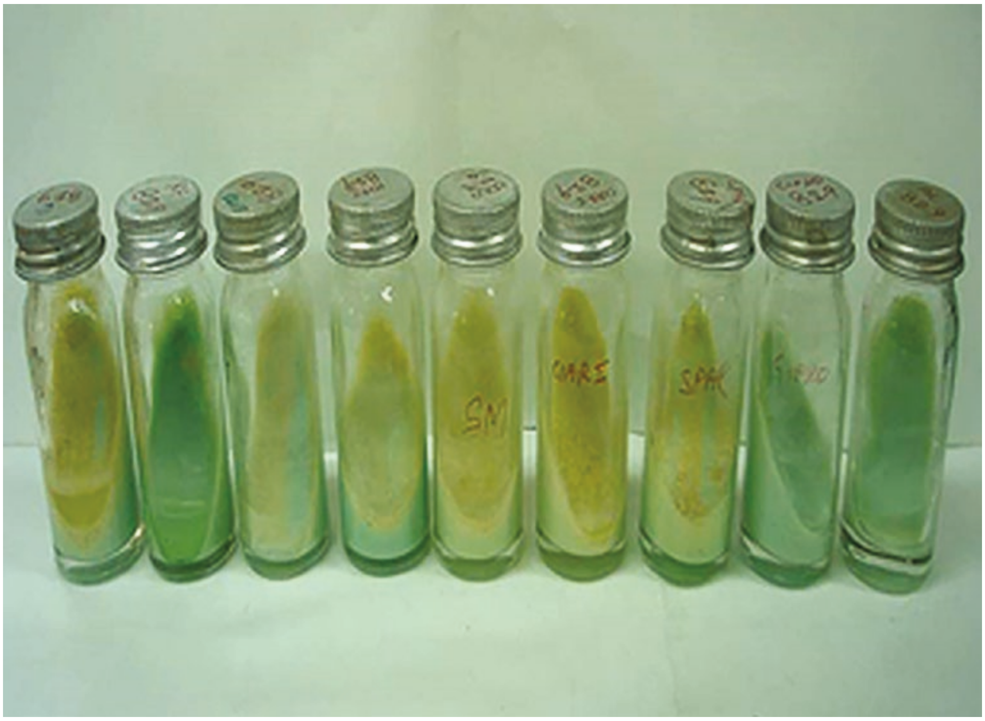


Fig. 8 The micro-broth dilution method for MIC testing

Fig. 9 Susceptibility testing for *Mycobacterium tuberculosis*. The absolute concentration method



5 Specific Recommendations for Major Infections

5.1 The Respiratory Tract

Respiratory tract cultures should be interpreted along with clinical and radiological findings. In non-neutropenic patients, the presence of significant numbers of pus cells (>25/lpf) in a Gram stain of the specimen is a useful indicator of an infection. If the results of culture are considered in isolation, then one ends up treating "bacteria" rather than an infection. Moreover, hospitalized patients, particularly critically ill patients, get colonized with hospital flora within 24 hours of hospitalization. The laboratory processes only specimens that are suggestive and representative of the lower respiratory tract. In case a patient is neutropenic, this needs to be indicated. Fungi like Candida are part of the normal flora and are not reported. It is essential to provide clinical information to facilitate appropriate processing and reporting.

Direct examination of samples is conducted for infections like Cryptococcus and acid-fast bacilli.

In critically ill patients, bronchoalveolar lavages or non-direct bronchoalveolar lavages (NDBALs) are sent. NDBAL samples are processed quantitatively. In fungal infections of the lung, a guided biopsy provides a tissue diagnosis. Tissues can be examined directly by the calcofluor stain for the demonstration of fungal mycelia.

5.2 Tissue Diagnosis

An oncology patient poses a diagnostic dilemma in several situations. Lung infections are a typical example of such a situation. It is often difficult to differentiate between a malignancy alone, a malignancy with an infection, or an infection alone.

Invasive tests may not be possible, and one may have to depend on specimens like bronchoalveolar lavages (BALs). Bronchoscopy, therefore, has a definitive role to play. A good BAL can thus clinch the diagnosis.

On rare occasions, it may be possible to perform an open lung biopsy. Many a times, material from suspicious lesions is collected only for histopathology (HP). The microbiologist will then have to depend on special stains and his/her own skills to provide a diagnosis of an infectious agent. It is possible to indicate the nature of the agent on histopathology; however, speciation and confirmation of the identity is only possible on culture. This is particularly so in the case of fungal pathogens when the histology section shows the presence of "fungal mycelia" which is a morphological diagnosis.

Some agents like Cryptococci can be diagnosed with a reasonable level of confidence on HP alone.

Cultures, however, remain the gold standard with all agents of infectious diseases. Lymph node lesions are another difficult situation where establishing the etiology of an infectious agent in the absence of a malignancy/metastasis is often elusive.

In cases with mycobacterial lymphadenopathy, direct visualization of acid-fast organisms is often negative. However, the majority of the aspirates/tissues in culture are known to yield positive results.

5.3 Fungal Infections

Fungal infections pose a major threat to cancer patients and remain a diagnostic dilemma for laboratories. A report of fungemia from the laboratory, i.e., the isolation of a fungus from a blood culture, should always be respected and treated with due concern.

Morphological diagnosis of a fungal infection should be supplemented with cultures. Not all fungi are responsive to antifungals. Moreover, antifungal drug resistance needs to be accounted for. Thus, diagnosis of a fungal infection in a cancer patient consists of a high index of clinical suspicion in patients with prolonged and profound neutropenia not responding to antibacterial agents.

Rapid assays for the detection of fungal antigens, galactomannan and beta-D-glucan assays, and nucleic acids by polymerase chain reactions (PCR) are also available for some common agents like yeasts and Aspergillus.

5.4 Blood Stream Infections

Blood culture is the most meaningful investigation, particularly in the febrile neutropenic patient. The recovery of microorganisms from blood in a bacteremic patient depends on the timing of the culture, ongoing antibiotics, method of collection, and method of processing.

It is mandatory to take aseptic precautions during collection; otherwise, one will isolate the contaminating skin flora.

There are several automated systems for the incubation of blood cultures, which reduce the time to detection of microbial growth in blood. Once there is a positive growth signal, the Gram stain indicates the type of organism, and direct susceptibility testing and identification can be performed. This reduces the reporting time by 12–24 hours. Separate media are available for bacteria, anaerobes, fungi, and Mycobacteria.

In patients with indwelling catheters, quantitative cultures from the peripheral vein and catheter are helpful in evaluating whether the catheter is a source of bacteremia. This can be proven if the same microorganism is isolated from the peripheral vein and the catheter with the pathogen growth at least two hours earlier from the catheter in paired blood cultures.

A blood culture yielding fungal growth is a certain test of a systemic fungal infection in a patient.

For detection of Aspergillus in blood, at least two (each 10 mL) aerobic blood cultures should be cultivated. If patients have a central venous access device, then cultures should be obtained through the catheter as well. In blood cultures, the chances of isolating yeasts are higher, detecting Candida species. in up to 60% of all fungemias within 2–5 days. Blood cultures have an extremely poor yield in patients with invasive aspergillosis, and the results are often negative even in patients with disseminated disease. Thus, a lack of positive culture does not rule out the diagnosis of invasive aspergillosis.

5.5 The Central Nervous System

Specimens of cerebrospinal fluid should be sent immediately to the laboratory. A direct examination of the sample by Gram stain indicates the likely organism in a case of bacterial meningitis. Examination with India ink showing negative staining of yeasts indicates cryptococcal meningitis. These samples can be processed for tests like adenosine deaminase for a presumptive diagnosis of tubercular meningitis.

5.6 The Urinary Tract

Urine samples must be transported to the laboratory within 3 hours of collection. The sample must be a mid-stream, clean-catch specimen, to avoid the contaminating genital flora. Urine is processed quantitatively, and only samples showing a significant number of polymorphs are processed for culture and those showing a colony count >10^5 cfu/mL, indicating significant bacteriuria, are reported.

5.7 Gastrointestinal Specimens

The commonest specimen is stool. Biopsies from the gastric mucosa are sent for cultures for *Helicobacter pylori.* A rapid urease test and Gram stain are the rapid tests for a presumptive diagnosis of *H. pylori*. Cultures are performed in special media and it takes 72 hours for the growth.

Stool specimens, which are watery or show pus cells, are processed for cultures for enteric pathogens. Surveillance cultures are performed for colonization with multidrug-resistant organisms to predict future episodes of infection and empiric treatment of febrile episodes.

6 Conclusions

There is a need for rapid and accurate diagnosis of infections in oncology, at the species level. The trend is changing and the pattern is different during the phases of treatment. Several emerging, new, and reemerging organisms are being documented as etiological agents. There is a need for tracking pathogens and susceptibilities. Multidrug-resistant isolates are on the rise. Antimicrobial resistance should be recognized as a serious problem and efforts taken to halt its growth. Given the relationship between antimicrobial resistance and use, antimicrobial stewardship is the logical first step to control antimicrobial resistance. Health-care facilities should decide on appropriate antimicrobial stewardship programs and diagnostic stewardship programs to pave the way for better outcomes.

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Imaging in Oncology

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1 Introduction

Imaging is a rapidly advancing field of medicine and is an integral part of cancer care. From its advent with a mere radiograph, an image formed by the projection of X-rays having passed through a part of the body, its role has exponentially gained momentum with numerous modalities being invented, such as ultrasonography (USG), which uses the principles of interaction of an ultrasound (US) beam with tissues in the body as it transmits through it, computerized tomography (CT), which uses a narrow beam of X-rays and an array of detectors, and magnetic resonance imaging (MRI), which is based on the effects of radio frequency and magnetism on the protons in the body. The radiograph itself has also gone through major technological evolution through computerization and digitization, leading to computerized radiography and digital radiography, thus easing the processing of acquired images, archiving data, and aiding in better imaging interpretation [1].

Imaging plays a role in detection, diagnosis, and staging as well as monitoring during treatment (response evaluation) and surveillance imaging. In the plethora of options available, it is important to understand which modality has to be used to answer a specific question at each step. In most cancers, imaging is quintessential prior to surgery and helps in planning exigent surgical procedures.

Each type of cancer has imaging integrated in its own specific way; however, in this chapter, we have disintegrated imaging in terms of modalities and briefly described the utility of each modality in modern cancer care.

2 Indications for Conventional Radiography in Oncology

Some notable indications for radiography in oncology are provided in Table 1. The most commonly performed radiography is that of the chest for evaluation of metastatic disease, anesthesia fitness, and pulmonary complications during treatment of cancer like infections, treatment-related toxicities, etc. Other indications for radiography are whole-body skeletal survey for multiple myeloma, spine radiographs for metastatic workup, and detecting the cause of backache/radiculopathy. To date, a radiograph of the bones remains the first and the most important investigation in the diagnosis of osseous lesions. Quite often, a radiograph is a modality to evaluate focal equivocal abnormalities that are detected on a bone scan, and it can help distinguish degenerative or metabolic abnormalities from neoplastic processes.

An orthopantomogram (OPG) is a special tomographic radiograph for the jaw, which is indicated in oncology for ruling out caries prior to initiation of radiotherapy for oral cancers and for evaluation of suspected osteoradionecrosis of the mandible.

Bedside radiographs constitute an important adjunct to patient management. These are useful for tracking the positions of lines and tubes in the body, the quantum of fluid

Table 1 Common indications of conventional radiography in oncology

Type of radiograph	Indications
Extremity and skeletal radiography	Detection of the pathology of the skeletal system such as primary bone tumor, secondary metastatic disease in bones, and pathological fractures (Fig. 1a)
Chest X-ray	Identification of lung diseases such as pneumonia, lung cancer, pulmonary edema, and metastatic disease in the lungs (Fig. 1b)
Abdominal X-ray	Detection of bowel (or intestinal) obstruction, free air (from visceral perforations) and organomegaly, abnormal calcifications, etc.

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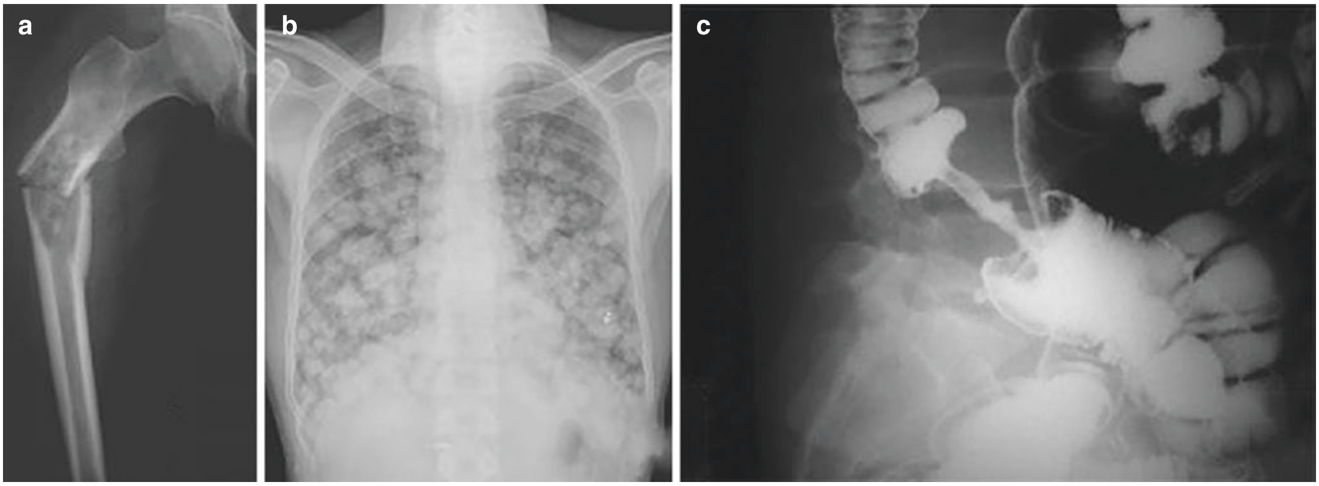

Fig. 1 (**a**) A radiograph of the right hip showing a pathological fracture in the proximal diaphysis of the right femur in an underlying expansile primary bone lesion. (**b**) A chest radiograph showing multiple canon ball opacities in the bilateral lung parenchyma (lung metastases). (**c**) Barium enema showing apple core deformity suggestive of colon cancer

collections such as effusions, and iatrogenic pneumothorax and iatrogenic emphysema. These also help in evaluating patients with acute abdominal pain, suspected to have intestinal obstruction.

Thus, despite the extensive use of cross-sectional imaging, a radiograph remains the persistent companion of nearly every patient in the oncology hospital.

3 Fluoroscopy and Contrast Studies

Fluoroscopy is another important technique in radiography, which is used to obtain real-time images of the internal structures of a patient with the use of radiographic contrast media to opacify the organs. Both the contrast media and its route of administration depend on the investigation. For example, oral administration outlines the lumen of the gastrointestinal tract (GIT), intravenous administration can delineate the kidneys, ureter, and bladder, the vascular tree can be delineated by intravascular (venous/arterial) administration, etc. It is now of immeasurable benefit in interventional radiology with its progress to image intensification and digital subtraction.

In the modern world of imaging, with the advent of newer modalities like CT scanning and MRI, the number and indications for fluoroscopic studies have significantly reduced (Table 2). However, there are few indications where these modalities may suffice for both diagnosis and treatment such as screening of cancers of the upper GIT and esophageal stent placement. When densities of the adjacent tissues are similar, a contrast agent is used to differentiate the surrounding structures. Structures typically requiring contrast instillation constitute the gastrointestinal and genitourinary system. Commonly used contrast agents are barium solution and water-soluble iodinated/noniodinated contrast agents. Barium is best used to visualize the gastrointestinal system; however, in certain conditions, there are some variations (see Table 2) [2].

Gas or air is also used for procedures like barium enema and loopograms to achieve double contrast and better delineation of the mucosa. If a bowel perforation or a leak is suspected, a water-soluble contrast agent is recommended because barium, if leaked, may cause barium peritonitis with sequelae of possible fibrosis/adhesions and small bowel obstruction. It is important to remember that in suspected cases of obstruction, barium enema is contraindicated as it may lead to barium impaction and further aggravate obstruction. On the other hand, in suspected cases of tracheoesophageal fistula or esophageal leaks, barium should be used rather than a water-soluble contrast agent as the contrast media can cause chemical irritation, whereas barium may not cause barium pneumonitis, if leaked in small quantity [2].

For non-gastrointestinal (GI) studies, iodine-based contrast agents are used. Certain sites in the body, however, cannot use these agents, such as the spinal canal for myelography (risk of neurotoxicity) or bronchial tree (risk of pulmonary edema). Nonionic contrast agents can be low-osmolar or iso-osmolar. Newer nonionic contrast agents have fewer adverse effects, are routinely used in most institutions, and are the first choice of contrast for pediatric and nephrology patients, the elderly, chronic diabetics, or for patients with borderline serum creatinine values [3].

Table 2 Common fluoroscopic studies with a contrast agent: indications and preparation

Region of interest	Study	Contrast agent	Indication	Preparation
Pharynx/esophagus	Barium swallow	Barium	• Stricture • Dysphagia • Hiatus hernia • Fistula • Diverticula • Inability to pass through an endoscope	In all, 6–8 h fasting Can have clear liquid
Stomach/duodenum	Barium meal	Barium	• Gastric ulcers • Gastric reflux • Tumors • Stricture • Diverticula	Overnight fasting
Small bowel loops	Barium meal follow through	Barium	Stricture Inflammatory/infective enteritis Diverticular disease Tumors	Overnight fasting Laxative—gut preparation
	Small bowel enema	Barium+ methylcellulose/ water	Precise localization of strictures Diverticular disease Enteritis Growth	
Large bowel loops	Barium enema (Fig. 1c)	Barium and air	Evaluation of the colon and rectum for strictures	Overnight fasting Laxative—gut preparation
Loopogram	Distal bowel loop	Water-soluble contrast or diluted barium	Pre-stoma closure to check the patency of the distal bowel and perforation	Nothing specific
Intravenous pyelography (IVP)	Kidneys; ureters	Water-soluble contrast	Ureteric obstruction Preoperative ureter mapping Postoperative ureteric leak Synchronous transitional cell carcinoma (TCC) with the bladder	Fasting 4–6 h Laxative—gut preparation
Micturating cystourethrography (MCU)	Urinary bladder Urethra	Water-soluble contrast	Postoperative evaluation Bladder outlet obstruction Hematuria Urethral stricture Recurrent urinary tract infection (UTI)	Nothing specific
Ascending urethrography	Urethra	Water-soluble contrast	Post-surgery Diverticulum, strictures Fistula Congenital anomalies	Nothing specific
Sialography	Salivary gland duct	Water-soluble contrast	• Obstruction • Ductal pattern • Post-radiotherapy • Functional integrity of glands	Nothing specific
Lymphangiography	Lymphatic system	Water-soluble contrast	Postoperative chyle leak Lymphatic obstruction	Nothing specific
Myelography	CSF space	Water-soluble contrast	Postoperative in case of artifacts on CT scan and MRI	Fasting 4 h

Special situation and preferred contrast:

- Esophageal perforation: water-soluble contrast
- Aspiration/fistula: barium or iso-osmolar water-soluble contrast
- Stomach/small and large bowel perforation: water-soluble contrast

4 Mammography

Mammography is a special low-dose radiography technique for evaluation of the breast tissue. The normal breast tissue consists of fibroglandular parenchyma and fat in varying proportions. Abnormalities in the breasts present primarily in the form of a mass lesion, microcalcifications, architectural distortion, or asymmetric density (Fig. 2). Microcalcifications that are detected on mammograms are less than a millimeter in size, and visualizing one from another requires an imaging technique, which has a high spatial resolution. The visual contrast between a normal and abnormal tissue varies from high to low depending upon the abnormality, e.g., microcalcifications are more radiopaque than the normal parenchyma but the lesions presenting as asymmetric densities or architectural distortions are not. Hence, this imaging technique has to have high contrast as well. These factors and the need to evaluate a superficial soft organ makes the mammography unit distinct from other radiography systems.

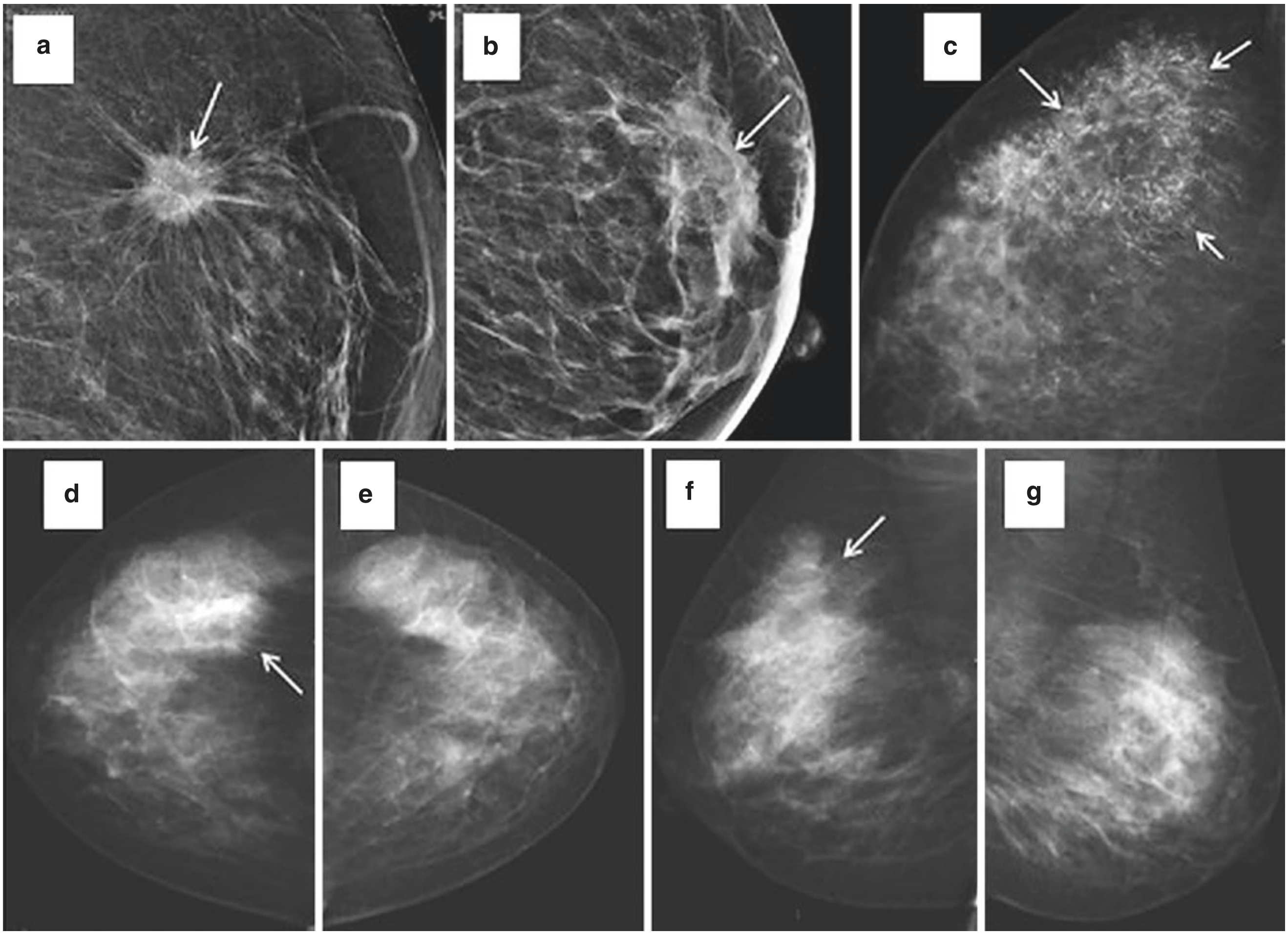

Fig. 2 Types of manifestations of breast cancer on mammograms. (**a**) A classic spiculated mass with microcalcifications (arrow). (**b**) An area of architectural distortion (arrow). (**c**) Regional branching pleomorphic microcalcifications (outer limits marked by arrows). (**d**–**g**) Different mammographic views of the right and left breasts of a patient showing asymmetric increased density in the right upper outer quadrant (**d**, **f**) marked by arrows

Today, mammography machines are available in screen film or analogue form and in digital systems. The advantage of the latter technique lies in improved dynamic range and contrast characteristics apart from the usual advantages of a digital technique like soft copy display, post-processing, transportability, and reduced rate of repeat radiographs for bad exposures. As such, a direct comparison of two techniques shows that the overall diagnostic accuracy of digital and film mammography for screening for breast cancer is similar, but digital mammography is more accurate in women under the age of 50 years, in women with dense breasts, and in premenopausal or perimenopausal women [4]. Digital breast tomosynthesis has been a recent modification in digital mammography, which allows multiple slices of the breast to be taken, like a CT scanner, thus reducing the problem of superimposition of tissues. This potentially helps in reducing recall rates and improving the cancer detection rate, but its benefit in terms of reduced mortality is not yet proven [5, 6]. Dual-energy subtraction and contrast-enhanced mammography are also advances in the mammography technique, which are being evaluated for use in clinical settings.

Mammography is performed in two scenarios: screening and diagnosis. Structured screening mammography programs are not available in India. Some earlier studies have shown an overall 15% reduction in breast cancer-related mortality (irrespective of the age of the patient) [7]. This comes at a cost of 30% in overdiagnosis and overtreatment. Currently, screening is offered to women who seek medical attention or to those who are at a high risk for breast cancer. The screening mammography units generally function independently from hospitals, and these mammograms are obtained in healthy women using two projections per breast and the studies are usually double read in batches. The women are then recalled if required for additional views or an ultrasound. Diagnostic mammograms are performed for women with signs and symptoms related to breast pathology. Indications include any clinical suspicion of a malignancy like a palpable lump, single-duct spontaneous nipple discharge, or nodularity/thickening. Often, additional views are obtained for suspected abnormalities, and an ultrasound may be performed for correlation, especially in women with dense breasts.

Mammography units are also used for performing guided interventions like stereotactic and tomosynthesis guided biopsies, hook-wire localizations, etc., for non-palpable lesions detected on mammograms and enhancing lesions detected only on contrast enhanced mammograms.

Standardized reporting formats like BI-RADS (Breast Imaging-Reporting and Data System) proposed by the American College of Radiology (ACR) have made a huge contribution in better acceptance of this modality and have paved the way for developing similar standardized formats for other organs like the prostate, liver, and thyroid.

5 Ultrasonography (USG) in Oncology

The advantages of USG are several: it is a quick study requiring almost no preparation, is also a "real-time evaluation" (also valuable for US-guided interventions like aspirations, biopsies, or injections) that is free of ionizing radiation, is widely available, and is portable. It is also relatively inexpensive compared to other modes of investigation. The biggest disadvantage of USG lies in the fact that it is operator-dependent. The documentation of abnormalities hence depends on the ability of the person performing the USG, and this cannot be subjected to review like radiographs or the cross-sectional modalities we are going to discuss later in this chapter.

Ultrasound is often the first investigation of choice when any abdominal mass/lesion is suspected. It helps in ruling out any developmental abnormalities, typically in children, or any functional cause that can mislead a clinician like an obstructed bladder mimicking a mass. It can also help in identifying masses and ordering the most suitable next line of investigations. It is also the first investigation for any small soft part imaging, like orbit, thyroid (Fig. 3), scrotum, soft tissue lesions of the limbs, and the breasts in younger women or in women with dense breasts on mammography. A real-time evaluation in combination with small maneuvers, like making the patient change dependent positions and combining it with Doppler, results in improved characterization of lesions.

The resolution offered by intra-cavitary USG like TVS (transvaginal ultrasound) or TRUS (transrectal ultrasound) makes US superior to CT scanning for characterization of uterine/pelvic lesions and the prostate.

Doppler evaluation for suspected deep or superficial venous thrombosis, suspected vaso-occlusive disease, problem solving for encasement versus contact between mass and major vessels, etc. are essential indications for ultrasound.

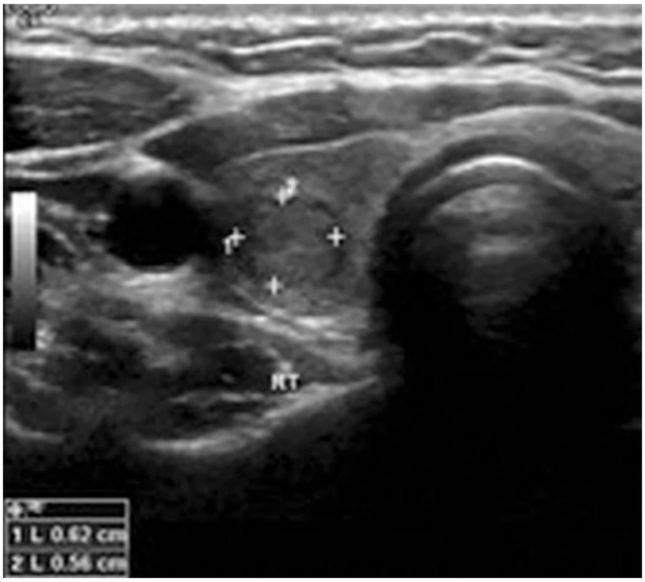

Fig. 3 Ultrasound of thyroid shows a circumscribed isoechoic nodule (bordered by + cursors) with a thin dark peripheral halo in the thyroid lobe on the right side of neck suggestive of a benign nodule

US is often performed for abdominal oncological emergencies like suspected torsion, tumor rupture, neutropenic colitis/typhlitis, evaluation of postoperative collections, etc.

Ultrasound is also the preferred modality for performing image-guided procedures like fine needle aspiration cytology (FNAC)/biopsies, drainage procedures like pleural or ascitic taps, pigtail placement in infected cavities/collections, etc.

Like portable radiographs, portable or bedside USG has become a part of standard of care in monitoring critical or sick patients in the intensive care unit (ICU).

6 Computed Tomography in Oncology

CT scanning is often considered as a workhorse of the oncological imaging department. It is not only used for diagnosis but also for staging of disease, assessing resectability, monitoring response to therapy, and in the follow-up after treatment. The important indications are displayed in Table 3.

CT angiography provides information on vascular involvement and preoperative vessel mapping, for detecting bleeders and thrombus. CT can also be used for guiding therapeutic procedures. Due to its multi-planar capability and recent advancement of CT softwares, various new applications can be obtained, which are shown in Table 4.

Table 3 Region-specific indications, area of coverage, and specific precautions/preparations for CT scanning

Region	Area of coverage	Indications
CT head (brain)	From the vertex to the base of the skull • Non-contrast scans • Contrast-enhanced scans	1. For diagnosis and follow-up of brain tumors and metastases (MRI is more accurate) 2. Acute intracranial hemorrhage and infarct 3. Effective in the detection of bone erosion 4. High Resolution Computed Tomography (HRCT) temporal bone for lesions involving the middle and inner ear along with involvement of the facial nerve pathway 5. Optimal visualization of the skull base foramina 6. Diagnosis and follow-up in patients with hydrocephalus
CT head and neck	From the skull base to the lung apices (should be covered up to the arch of the aorta if CT angiography of the neck is requested or if vocal cord palsy is being investigated) • Non-contrast scans (select indications) • Contrast-enhanced scans	Staging of tumors of 1. The nasal cavity and paranasal sinuses (MRI is preferred for perineural spread and to distinguish between tumor and secretions) 2. Pharynx (MRI is preferred for the nasopharynx) 3. Gingiva and buccal mucosa, specially for evaluating the mandible 4. Floor of the mouth and tongue (MRI is more accurate) 5. Orbital tumors 6. External ear evaluation 7. Salivary glands (MRI is preferred) 8. Larynx and hypopharynx 9. Thyroid and parathyroid glands 10. Upper trachea 11. Parapharyngeal masses (paragangliomas and schwannomas) 12. Bony tumors of the mandible, maxilla, and hyoid bones
CT thorax	From the nape of the neck up to the costophrenic recess (lower part) • Non-contrast scans • Contrast-enhanced scans	Detection, staging, and follow-up of tumors of 1. The lung (MRI is preferred in superior sulcus tumors) 2. Esophagus 3. Pleural tumors 4. Mediastinal masses 5. Breast masses 6. Rare tumors of the heart, aorta, and inferior vena cava (IVC) Detection and characterization of the mediastinal, hilar, or axillary adenopathy in cases of known malignancy Detection and characterization of the skeletal lesions (ribs, vertebrae, sternum, clavicle) Detection and follow-up of lung metastases Infective lung pathologies (patients on chemotherapy are prone to fungal pneumonia) CT bronchoscopy is a noninvasive technique to get virtual pictures of the airways Postoperative esophageal/anastomosis leak Diagnosis and follow-up of pleural/pericardial effusions
CT abdomen and pelvis	• From the dome of the diaphragm to the ischial tuberosities • Non-contrast scans followed by contrast-enhanced CT scans	Detection, staging, and follow-up of tumors of 1. Liver 2. Gall bladder and biliary tract 3. Pancreas and spleen 4. Stomach, small and large bowel (including GISTs and neuroendocrine tumors) 5. Rectum and anal canal 6. Prostate and seminal vesicles 7. Uterus, cervix, vagina, and vulva (MRI pelvis is more accurate for local evaluation for 5, 6, and 7) 8. Kidneys, ureters, urinary bladder, and urethra 9. Peritoneal masses 10. Retroperitoneal masses 11. Bone neoplasms and metastases (vertebrae, pelvic bones, proximal femora) Diagnosis and follow-up of secondaries in the liver, spleen, retroperitoneum, and peritoneum Diagnosis and follow-up of ascites, localized collection and lymphoceles Post-surgery bowel obstruction/ischemia
Therapy and guidance with CT scanning		1. Biopsy and aspiration 2. Pigtail catheterization 3. Nephrostomy catheter placement 4. Radio-frequency ablation 5. Radiotherapy instrument placement

Table 3 (continued)

Region	Area of coverage	Indications
Common acute indication in an oncology hospital		1. Brain metastases/hemorrhage/infarct 2. Pulmonary thrombus 3. Fungal pneumonia 4. Fluid collections and aspirations 5. Bleeder detection for drop in hemoglobin, hematemesis, hemoptysis, malaena, etc. 6. Bowel obstruction, ischemia

MRI is a better modality for evaluating pelvic structures, including the uterus, ovaries, and vagina in females and the prostate and seminal vesicles in males. Local staging of rectal and anal canal cancers is best performed with MRI. Bone and soft tissue tumors are well-characterized on MRI. MRI is a standard modality of choice for characterization of brain tumors, bone tumors, few head and neck tumors, and even for hepatic malignancies

Table 4 Additional applications of CT

Technique	Advantage	Additional scans if required
3D planar reconstruction and volume rendering technique (VRT)	Viewing of the obtained data in all three planes (axial, sagittal, and coronal) with formation of a 3D image of the organ of interest	No
Maximum intensity projection	Good for visualization of the objects having higher density, e.g., vessels in angiography	No
CT volumetry	To obtain an approximate volume of the tumor/fluid collection, which aids in treatment planning	No
CT colonoscopy	• A noninvasive screening tool for colorectal carcinoma • Provides a virtual picture of the entire colon • Detection of more than 6-mm polyps is similar to the results of colonoscopy	An additional prone non-contrast scan with air inflation of the rectum is required
CT bronchoscopy	• Can visualize the tracheobronchial lumen, cartilage rings, and carina, down to the fourth-order bronchial orifices and mimics optical bronchoscopy • This noninvasive modality is highly sensitive to detecting bronchial masses and, along with multiplanar reconstruction, can delineate extraluminal tumor extension (less sensitive in picking mucosal lesions)	No
CT cisternography	Visualization of CSF spaces and cisterns for detection of CSF leaks	An additional prone scan of the peripheral nervous system (PNS) has to be obtained after injection of diluted intravenous (IV) contrast in the subarachnoid space via a lumbar puncture
CT enteroclysis	• Mainly performed to evaluate disease of the small bowel, and it compliments the findings of capsule endoscopy • It is highly sensitive as compared to conventional enteroclysis in detecting inflammatory bowel disease, unexplained gastrointestinal bleeding, and small bowel obstruction along with extraluminal information	No additional scan is required; however, a negative contrast agent that distends the bowel, e.g., mannitol, needs to be administered prior to examination

7 Magnetic Resonance Imaging in Oncology

MRI is one major advance in imaging, which distinguishes itself not only because of lack of ionizing radiation but also because of superior soft tissue resolution and characterization. It helps in characterization of lesions by utilizing the differences in the relaxation times of various tissues, functional aspects such as cellularity, perfusion, angiogenesis, and even metabolite levels in some cases. The widely used applications of MRI have been described in Table 5.

Table 5 Clinical indications and utility of MRI in various regions

Region	Key points	MR pulse sequences/protocol and clinical utility
Brain and spine	MRI helps diagnose a space-occupying lesion and characterizes it as a tumor, depicting its morphology, extent and grade, and prognosis It can help choose an appropriate site for biopsy and assess response, thus differentiating progression from pseudoprogression	Conventional magnetic resonance imaging (MRI) is better than CT in both diagnosis and anatomical details. The sequences used are T1-weighted (T1W), T2-weighted (T2W), fluid-attenuated inversion recovery (FLAIR), and contrast-enhanced sequences. Use of advanced techniques including diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS) perfusion-weighted (PW) imaging, and dynamic contrast enhanced (DCE) MRI provide functional information beyond anatomy and have been commonly used in clinical practice Apparent diffusion coefficient (ADC) maps, fractional anisotropy (FA), cerebral blood flow (CBF), relative cerebral blood volume (rCBV), MR spectroscopy (MRS), and permeability maps may enable identification and differentiation of tumor types, its grade, extent, guide biopsy, and predict early response to treatment
Head and neck	MRI is more accurate in the local staging of cancers of the nasopharynx, oropharynx, salivary glands, nasal cavity, paranasal sinuses, oral tongue, and floor of the mouth Perineural spread, intracranial invasion, dural spread, and retropharyngeal adenopathy are best assessed by MRI. Distinguishing between sinus secretions and tumor, and differentiating between posttreatment changes and residual disease are some of the advantages of MRI	Thinner slices (<3 mm) are important for coronal or sagittal reconstruction because invasion patterns are best appreciated in the nonaxial plane
Orbit	Evaluation of ocular and extraocular tumors, local staging of retinoblastoma (Fig. 4), and optic nerve lesions	T1, T2, post-contrast images with small FOV and planning of sagittal images along the course of the optic nerve for each eye
Chest Mediastinal masses Chest wall masses	MRI enables superior tissue characterization of mediastinal masses with high diagnostic specificity MRI helps differentiate cystic and solid components as well as contents such as fat, hemorrhage, proteins, and fibrosis and also prevents unnecessary diagnostic intervention by characterizing benign findings and improves diagnostic yield by guiding the appropriate site for biopsy Guides the surgeon by depicting the anatomy for planning resection Differentiate malignant from benign osseous tumours and characterise soft tissue tumors MRI is superior to CT in detecting chest wall invasion, particularly in Pancoast tumors	T1W, T2W, Short Tau Inversion Recovery (STIR), DWI, and T2W fat-saturated pulse sequences to differentiate between solid, cystic, proteinaceous, fatty or hemorrhagic lesions and planes with mediastinal structures Pre-gadolinium and post-gadolinium 3D GR DCE sequences for paragangliomas and hemangiomas Ultrafast GRE in-phase (IP) and out-of-phase (OP) chemical shift sequence to see the presence or absence of microscopic or intravoxel fat within a lesion Routine T1W, T2W, STIR, and post-contrast T1W sequences Parallel MRI with high temporal resolution cine imaging, such as steady-state free precession (SSFP) may reveal subtle invasion of mediastinal structures and the chest wall
Body Hepatobiliary and pancreas	MRI is the most superior imaging technique for diagnosis and presurgical planning for hepatobiliary and pancreatic malignancies DCE MRI is the modality of choice for detection and characterization of nodules detected at screening; for staging hepatocellular carcinoma (HCC) as well for surveillance, and follow-up MRI is highly specific for HCC and can avoid an unnecessary biopsy in underlying cirrhosis Newer imaging techniques, including hepatocyte-specific contrast agents and diffusion-weighted imaging, may further improve MRI imaging sensitivity to HCC	SSFSE heavily T2-W sequence-characterises cysts, collections and edema. Hemangiomas too appear bright on this sequence The BSSFP sequence—rapid motion-insensitive bright blood sequence—helps in delineating the vessels, ducts, bowel loops, and fluid collections In-phase and out-of-phase dual GRE (dual fast field echo) for tissue characterization provides sensitivity to microscopic fat (hepatic steatosis, hepatic adenoma, or hepatocellular carcinoma). Susceptibility artifact (detecting iron in abdominal organs, air secondary to disease), and other agents of a low T1 value Dynamic multiphasic 3D fat-suppressed spoiled gradient echo (3D GRE) sequence aids in MRI of the liver, characterizing normal parenchyma from lesions, and delineates vascular structures Hepatocyte-specific contrast agent (HSCAs)-based 3D fat-suppressed spoiled GRE sequences for specific indications Diffusion-weighted imaging (DWI) for solid liver lesions and monitoring response to treatment

Region	Key points	MR pulse sequences/protocol and clinical utility
Prostate	MRI helps in detecting clinically significant cancers, assists in targeting lesions, as cognitive or software fusion, or by MRI-guided biopsies, improving accuracy and selection of higher Gleason-grade lesions It also plays a role in triaging patients for active surveillance	Multiparametric MRI of the prostate offers excellent soft tissue anatomy for different parts of the gland on high-resolution T2W sequences, with superadded functional evaluation from diffusion-weighted imaging (DWI), dynamic post-contrast enhanced imaging (DCE), and optional MR spectroscopy (MRS)
Rectum	Optimal local staging in rectal cancer is performed with MRI by defining the pertinent anatomy of the rectum and showing relation to the surrounding organs and mesorectal fascia. MRI helps decide the need for preoperative chemoradiotherapy, plan surgery, and estimate prognosis	T2-weighted magnetic resonance imaging with small field of view and high resolution is now the first-line imaging tool for evaluation and guiding management for rectal tumors DWI can help in monitoring response to chemoradiation
Bone and soft tissue	MRI is the examination of choice for local staging (intraosseous, extraosseous, neurovascular bundle, and joint involvement), for determining the target and the course of the biopsy tract, and for surgical planning. The entire bone should be scanned including the proximal and distal joints to evaluate for skip metastases MRI, due to its inherent capability to characterize soft tissue, is the preferred modality for soft tissue tumors and tumor-like conditions	STIR is the initial imaging sequence for further planning The T1W sequence is best to show the marrow extent and skip metastases Lobular high-T2-pattern signal intensity is specific for chondroid origin lesions because of the inherent increased water content in the cartilages At least two orthogonal planes, with one being axial plane, should be planned on an MRI T1W and T2W sequences should be obtained because most soft tissue lesions have been described with their spin echo (SE) T1W and T2W signal characteristics DCE sequences by virtue of differential enhancement can differentiate the etiology of benign from that of malignant to some extent but may not always obviate the need for a biopsy
Breast	Adjunct to mammography and USG breast. Some common indications include evaluation of lobular cancers, unknown primary with limited sites of metastases to the axilla and suspected primary in breast, Paget's disease with no abnormality on mammography, patients undergoing partial breast irradiation following a breast conservation surgery, and patients with highly dense breasts for local disease evaluation	Plain T2W/STIR, DWI, and plain T1W (optional) followed by dynamic post-contrast images obtained after a rapid bolus of contrast injection using a gradient echo sequence Subtracted images to be viewed on monitors along with time–intensity curves
Miscellaneous	The pancreatico-biliary drainage system (MRCP) pelvicalyceal system and ureters (MR urography), and other fluid-filled ductal systems are extremely well-visualized without need for a contrast agent	Heavily T2-weighted sequences

3D three-dimensional, *GRE* gradient echo, *DCE* dynamic contrast-enhanced (DCE) imaging, *IP* in-phase, *OP* out-of-phase, *BSSFP* balanced steady-state free precession, *SSFSE* single-shot fast-spin echo, fat-suppressed 3D GRE sequences include LAVA (liver acquisition with volume acceleration), *LAVA-Flex* liver acquisition with volume acceleration-flexible, *THRIVE* T1 high-resolution isotropic volume excitation, *mDIXON* modified Dixon, *VIBE* volumetric interpolated breath-hold examination, *FOV* field of view (FOV)

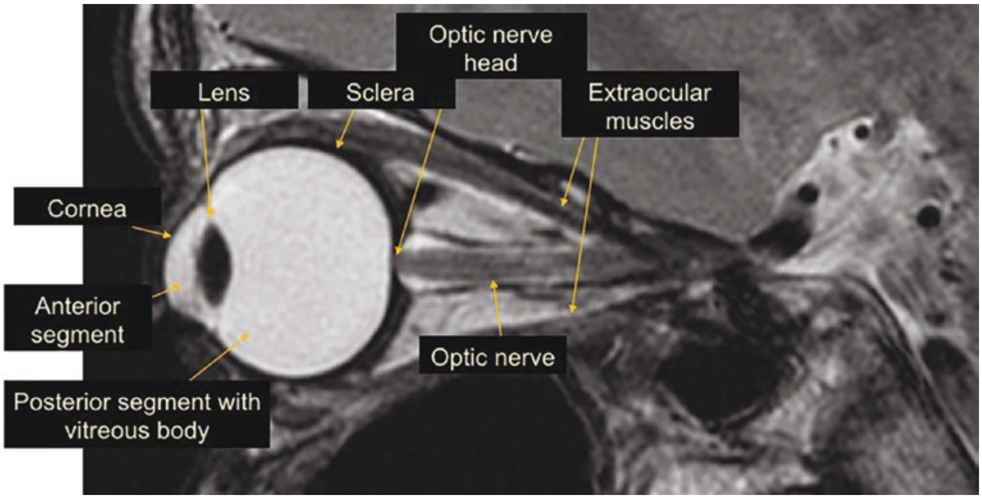

Fig. 4 Sagittal T2W MRI image of the orbit shows the detailed anatomy of the globe and optic nerve

8 Response Evaluation in Oncology

The RECIST (Response Evaluation Criteria in Solid Tumors) criteria, introduced in 2000 and updated (RECIST 1.1) in 2009 are the workhorse for response assessment in most clinical drug trials [8]. These provide guidelines for technical parameters required for imaging cancer patients on trials, how to select and measure the lesions using the single longest diameter, and how to calculate response. RECIST 1.1 defines how to differentiate measurable lesions (broadly, lesions more than 1 cm in size or nodes more than 15 mm in a short-axis diameter on cross-sectional imaging) from nonmeasurable lesions (lesions less than the above size, as also effusion, ascites, peritoneal nodularity, leptomeningeal metastases, bony metastases without a soft tissue component, and other such examples). Up to five lesions on the baseline scan are to be selected as target lesions, with the sum of the longest diameters used for response assessment. Disappearance of all lesions is considered complete response (CR), ≥30% decrease is considered partial response (PR), ≥20% increase is considered progressive disease (PD), whereas anything in between is considered stable disease (SD). Appearance of a new measurable lesion or unequivocal progression of nonmeasurable disease is also considered PD.

The size-based RECIST criteria are, however, found lacking in assessing response to newer treatments and also for assessing specific cancers such as gliomas, and multiple alternate response criteria have also emerged for specific usage. These include the Choi criteria for use in patients on targeted therapy (classically gastrointestinal stromal tumor (GIST) patients on imatinib) [9], iRECIST [10] criteria for patients on immunotherapy, RANO (Response Evaluation in Neuro-oncology) criteria for gliomas, Deauville criteria for lymphomas, mRECIST criteria for hepatocellular carcinomas, and PERCIST (Positron Emission Tomography Response Criteria in Solid Tumors) criteria for PET/CT assessment of response.

9 Molecular and Functional Imaging in Oncology

MRI technology has not only helped in anatomical soft tissue characterization and delineation of abnormalities but has also taken imaging to the functional and cellular levels using various techniques such as perfusion, vascular permeability, tissue oxygenation [blood oxygenation-level dependent (BOLD) technique] [11] and cellular status, density, and microstructural organization (diffusion technique) [12, 13].

Molecular diffusion is a reflection of the free Brownian motion in the cellular microenvironment, based on media viscosity, temperature, molecular mass, and the value measured as apparent diffusion coefficient (ADC) [14]. Tumor ADC maps help in differentiating enhancing lesions, peritumoral edema, and cystic/necrotic changes from the surrounding structures. It aids in characterization, assessment of the grade of tumor, tumor cellularity, and response to chemotherapy.

Use of imaging biomarkers for assessment of tumor angiogenesis is on the rise for understanding the effect and activity of the pharmacodynamics of the drugs used. Dynamic contrast-enhanced MRI assesses tumor pathophysiology, response assessment to radiotherapy, and antiangiogenic agents. Intravenous contrast gadolinium, once injected, with subsequent acquisition of serial dynamic images, based on a compartment model (accounting for tissue perfusion and vascular space), generates a set of parameters such as blood flow, blood volume, vessel permeability, and extracellular extravascular space [15]. Perfusion kinetics are often used for determining residual/recurrence disease and response assessment in addition to morphological imaging.

MR spectroscopy (MRS) detects tissue metabolites containing protons [16], phosphorus, or enriched carbon [17]. Proton MRS has a promising role in guiding biopsies in organs such as the brain, breasts, and prostate, based on the choline:creatinine ratios. Decrease in choline levels may also be seen as a response to therapy.

Molecular functional imaging (MFI) techniques are used in addition to anatomical delineation, forming an essential part of cancer management, providing metabolic and functional information. These have been briefly summarized in Table 6.

Table 6 Molecular imaging techniques: principle and applications

Imaging technique	Principle	Applications
Contrast-enhanced ultrasound	Gas-filled microbubbles are used as contrast media. They are intravenously introduced into the systemic circulation, enabling the visualization of tissue vascularity and perfusion on real-time ultrasound	1. Measuring blood volume and perfusion 2. Lesion characterization—benign vs. malignant 3. Gene delivery and drug delivery—future applications
Ultrasound elastography	Cancer tissues, by virtue of their cellularity and desmoplasia, are more stiffer than are normal tissues and most benign lesions. A measure of elasticity, perceived by the extent of deformation of ultrasound waves, helps estimate the likelihood of a malignancy	1. Differentiating benign from malignant lesions, particularly in the breast, liver, prostate, and thyroid
Computed tomography (CT) perfusion imaging	It provides information about hemodynamics at the capillary level of various tissues. Monitoring the first pass of an iodinated contrast agent bolus through the organ of interest can determine perfusion	1. Differentiating benign from malignant lesions on the basis of the components of angiogenesis 2. Help in guiding biopsy by highlighting the area with higher angiogenesis, thus increasing the likelihood of a core with a better diagnostic yield 3. It can help monitor the response to therapy
Computed tomography (CT) texture analysis	The texture concept in a CT image is the distribution of gray-level values (or heterogeneity) in the region of interest in an image. CT texture analysis objectively measures the amount of heterogeneity in a given tissue, with the data represented as a statistical chart	1. Texture analysis of cervical cancer, colon cancer, and lung cancer helps differentiating from benign conditions. It also helps in response assessment 2. Utility as an imaging-based biomarker for gene expression
Positron emission tomography (PET)	It is a functional imaging modality, which detects 1. Blood flow 2. Glucose metabolism 3. Receptor density A radioactive tracer is intravenously injected. The tracer is taken up by the tissue of interest. The tracer decays and emits a positron, which itself, on further decay, emits a pair of gamma rays. These gamma rays are detected by a scintillator, with post-processing software generating a medical image	1. Workhorse for functional oncological imaging in detecting primary disease, recurrent disease, nodal involvement, and metastatic disease and in assessing response to therapy. Used as a cancer-staging modality 2. It is also used prior to stereotactic surgery to guide the resection of brain tumors
Single photon emission computed tomography (SPECT)	In SPECT, a gamma ray-emitting radioactive substance (most commonly used: technetium) is intravenously injected and imaging is performed using a gamma camera. Radioactive substance concentration in the tissue of interest and three-dimensional information regarding the tissue of interest are detected by the camera	1. Bone scan for metastatic bone disease, metabolic disorders, etc. 2. Sestamibi scan for parathyroid disorders 3. Metaiodobenzylguanidine (MIBG) imaging and therapy for neuroblastoma 4. Peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumors
Magnetic resonance spectroscopy (MRS)	Magnetic resonance spectroscopy (MRS) quantifies levels of metabolites in body tissues after fat and water suppression. The MR signal amplifies the microquantities of the titers of these metabolites, thus producing a spectrum of resonances. Fluctuations in these metabolites reflect a pathology. For example, choline is a primary phospholipid of the cell membrane, and thereby, an increase in its concentration reflects greater cell division, as seen in malignancies. In lesions of a neuroparenchymal origin, this is accompanied by reduced *N*-acetyl aspartate due to neuronal loss. Increased lactate levels reflect the anaerobic processes in malignancies or infections. Citrate is a normal component of prostate cells and, similarly, its levels are decreased in prostate cancer	1. Characterization of brain tumors, benign pathologies, infective lesions, etc. It may provide an insight into differentiating from tumor mimics such as tuberculosis and fungal etiology, in assessment of tumor progression from pseudoprogression and radiation necrosis 2. It is also used for detection of carcinoma of the prostate 3. Other applications include breast cancer and cervix cancer
MRI diffusion-weighted imaging (DWI)	The movement of free water molecules in extracellular space is restricted in an environment with many more cells in number and larger sizes of cells, both associated with cancer cells, and few pathological conditions like abscesses. This, in turn, can restrict the movement of water molecules in biological tissues. Changes in tumor cellularity and cell membrane integrity can be estimated qualitatively and quantitatively	1. Diagnosis of acute stroke 2. Characterizing brain tumors and certain infective lesions 3. Assessing response to treatment of tumors in various organs throughout the body

(continued)

Table 6 (continued)

Imaging technique	Principle	Applications
Magnetic resonance perfusion imaging	Perfusion-weighted imaging reflects the vascular perfusion of organs and tissues. It detects angiogenesis as well as predicts and quantifies the response to antiangiogenic therapy. Angiogenic blood vessels are more permeable than are normal vessels, thereby allowing contrast passage into the tissues. First, T1-weighted dynamic contrast-enhanced imaging determines leakage from permeable blood vessels as a surrogate marker for angiogenesis. Second, the T2*-weighted sequence for dynamic susceptibility contrast imaging measures the relative blood volume (rBV) corresponding to capillary density, reflecting the tumor grade	1. Primarily, perfusion imaging evaluates ischemic conditions such as acute cerebral infarction where identifying the ischemic penumbra can help in patient management and in conditions like Moyamoya disease 2. Grading of tumors such as diffuse astrocytomas often simulate higher values of perfusion 3. Assessment of response, determining residual disease, and recurrence
Functional MRI (fMRI): BOLD and hypoxia imaging	Functional MRI (fMRI) measures neuronal activity-induced signal changes, where increased activity results in increased vascularity, greater influx of oxyhemoglobin (more than that required for metabolism), and relative decrease in deoxyhemoglobin. The latter is paramagnetic, and, hence, its decreased level increases the magnetic signal intensity. This is called the BOLD (blood oxygen-level dependent) effect The presence of hypoxia contributes to poor prognosis, with important consequences for diagnosis and treatment. For example, the oxygenation status in cervical cancer is independent of size, stage, pathological type, or grade of the tumor	1. Planning neurosurgery to assess which regions can be excised without compromising the patient's neuronal status 2. Mapping the location of tumors, extent of stroke and head injuries, and conditions like Alzheimer's, where the epicenter of the pathology and its adjoining effect can be neurologically mapped for estimated deficit 3. In psychiatry for behavioral therapy and assessing response to it 4. Hypoxia imaging in tumors
Ultrasmall particle iron oxide (USPIO) MRI	USPIO developed for MRI of the reticulo-endothelial system (lymph nodes and liver), causes signal drop on T2* imaging. Accumulation of iron oxide nanoparticles in macrophages is the basis for nodal imaging with dextran-coated USPIO agents	It is used to distinguish metastatic lymph nodes that may not be morphologically abnormal in size or to differentiate enlarged metastatic nodes from enlarged reactive/benign hyperplastic nodes
MR elastography	Magnetic resonance elastography (MRE), a novel imaging method synchronizes motion-sensitive phase-contrast MR sequences to application of acoustic waves. Mechanical waves are propagated using MRI for quantitative stiffness information, especially in anatomically inaccessible sites such as the brain	

10 Conclusions

To summarize, imaging plays a vital and specific role in delivering optimal care in oncology. A sound knowledge of the pros and cons of different imaging techniques can help in choosing the optimal modality for a given patient.

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Nuclear Medicine in Oncology

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Abbreviations

ATA	American Thyroid Association
CEA	Carcinoembryonic antigen
CT	Computed tomography
DTC	Differentiated thyroid cancer
^{18}F-FDG	[^{18}F]Fluorodeoxyglucose
F18 FET	^{18}F-Fluoro-ethyl-tyrosine
FLT	3′-Deoxy-3′-^{18}F fluorothymidine
GIST	Gastrointestinal stromal tumor
LAT1	L-type amino acid transporter 1
MIBG	Metaiodobenzylguanindine
MRI	Magnetic resonance imaging
NaF	Sodium fluoride
NIS	Sodium iodide symporter
PET	Positron emission tomography
PSMA	Prostate-specific membrane antigen
RAI	Radioactive iodine
SPECT	Single photon emission computed tomography
SRI	Somatostatin receptor imaging

1 History

Nuclear medicine involves the administration of a fixed amount of radiolabeled pharmaceuticals to the patient with the intention of providing therapy and diagnosis. Nuclear medicine can be considered to have originated with the discovery of radioactivity itself as a result of the works of Dr. Henry Becquerel and Marie Currie [1]. It really took off with the invention of the cyclotron by Ernest Orlando Lawrence in 1930 [2]. However, we had to wait until the 1950s to acquire the technologies that could obtain images of radioactivity distribution in the body. The first of such technologies was invented by Benedict Cassen with the development of a rectilinear scanner in 1951 [3]. Then came the Anger camera, developed by Haul Anger in 1958, who is considered the forefather of all other gamma cameras to follow [4]. In 1951, Wrenn and coworkers discovered the favorable imaging characteristics of positron-emitting radioisotopes [5].

Iodine-131 (I-131) had been the foremost radioisotope used in medicine for a long time, which changed in 1964 when Paul Harper started using technetium-99m (Tc99m) for imaging [6]. Tc99m proved to be an excellent agent for imaging. Gamma rays emitted by Tc99m have favorable imaging properties, and, being chemically versatile, Tc can label a huge number of pharmaceuticals.

Initial gamma camera imaging was planar, which did not offer good resolution and anatomical localization; however, technologies for tomographic reconstruction have significantly changed this. This led to the development of positron emission tomography (PET) imaging by Phelps et al. [7] and single photon emission computed tomography (SPECT) by Kuhl et al. in 1970s [8]. PET imaging has become ubiquitous in medical practice; this is primarily due to the advent of the metabolic tracer [^{18}F]fluorodeoxyglucose (^{18}F-FDG). Finally, the advent of fusion imaging modalities such as PET/computed tomography (CT) and SPECT/CT has revolutionized diagnostic imaging, especially in oncology.

Use of radioisotopes in therapy is even older than imaging. In the early 1940s, iodine-131 (I-131) was successfully used to treat metastatic follicular thyroid cancer. Phosphorus-32 (P-32) was the first radionuclide used for cancer treatment of leukemia and polycythemia vera. From the era of P-32 and I-131, we have now come to the era of lutetium-177 (Lu-177), a versatile tracer that can be tagged with a plethora of pharmaceuticals and can be used for therapy.

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2 Radiopharmaceuticals

A radiopharmaceutical is a chemical compound that has been tagged with a suitable radioisotope. These chemicals, after administration, get localized to specific organs or disease sites in the body depending on their specific pharmacodynamic and pharmacokinetic properties and emit radiations of various types. Thus, they can portray physiology, biochemistry, or pathology within the body. Depending on the emitted radiation, a particular radiopharmaceutical can be used for either diagnosis or therapy. The radiopharmaceuticals that emit non-particulate electromagnetic radiations like gamma (γ) rays can be used for diagnostic imaging, whereas the ones emitting particulate radiation such as alpha (α) and beta (β) are used for therapeutic purposes. Each radiopharmaceutical will have a specific decay characteristic and half-life of the tagged radioisotope. Radioisotopes for therapy and diagnosis are produced by three main methods: nuclear reactor, cyclotron, or on-site generator systems. Generators such as molybdenum–technetium (Mo-Tc) generators and germanium–gallium (Ge-Ga) generators are enabling nuclear medicine departments to produce important radiopharmaceuticals on-site. Few of the most commonly used radiopharmaceuticals with their clinical uses are summarized in Tables 1, 2, and 3.

Table 1 Gamma camera radiopharmaceuticals

Radiopharmaceutical	Physiological principle	Clinical use
Tc^{99m} MDP	Bone turnover	Skeletal metastasis, primary bone tumor, arthritis
Tc^{99m} DTPA	Glomerular filtration	Renal function (GFR) and drainage
Tc^{99m} EC	Tubular secretion	Renal function and drainage
Tc^{99m} DMSA	Cortical fixation	Renal scars
Tc^{99m} sestamibi	Myocardial perfusion	Coronary artery disease—reversible ischemia
Tl^{201} chloride	Myocardial perfusion	Coronary artery disease—reversible ischemia and myocardial viability
Tc^{99m} ECD	Brain perfusion	Epilepsy, dementia
Tc^{99m} MAA	Lung perfusion	Pulmonary embolism
Ga^{67} citrate	Iron-binding protein	Tumor imaging, infection imaging
NaI^{123}	Sodium iodine symporter (NIS)	Thyroid imaging—benign and malignant diseases
I^{123} MIBG	Presynaptic uptake	Neural crest tumors
In^{111}-labeled leukocytes	Chemotaxis	Infection imaging

Table 2 PET radiopharmaceuticals

Radiopharmaceutical	Physiological principle	Clinical use
F^{18} FDG	Glucose metabolism	Tumor imaging, infection, and inflammation imaging
F^{18} NaF	Bone turnover	Bone metastasis, primary bone tumor
Ga^{68} PSMA	Receptor imaging	Prostate carcinoma
Ga^{68} DOTA-NOC	Receptor imaging	Neuroendocrine tumor
Rb^{82} chloride	Myocardial perfusion	Coronary artery disease—quantification of myocardial blood flow

Table 3 Therapeutic radiopharmaceuticals

Radiopharmaceutical	Physiological principle	Clinical use
NaI^{131}	Sodium iodine symporter (NIS)	Carcinoma thyroid, Grave's disease, toxic multinodular goiter
Sm^{153} EDTMP	Bone turnover	Palliation of metastatic bone tumor
I^{131} MIBG	Presynaptic uptake	Neuroectodermal tumors
Lu^{177} DOTATATE	SSTR receptor (PRRT)	Neuroendocrine tumors
Y^{90} spheres	Transarterial radioembolization (TARE)	HCC, metastatic liver cancer
Re^{186} colloid	Intrasynovial injection (radiosynovectomy)	Rheumatoid arthritis

3 Positron Emission Tomography (PET)

Positron emission tomography using positron-emitting radiopharmaceuticals has revolutionized diagnostic imaging in clinical oncology. This special characteristic of positron emission is utilized in a special capacity for imaging. A positron, after being emitted by a radioactive nucleus, interacts with a local electron to produce a pair of annihilation photons, which, when emitted in an opposite direction on being detected by a circular array of scintillation detectors create a coincidence event [9]. This is known as annihilation coincidence detection (ACD). This method is successfully utilized to detect positron distribution in an injected patient. Along with ACD, some PET cameras are now using a newer technology, eponymously named time of flight (TOF). This technology has improved the resolution of PET systems. A PET system provides not only better resolution but also better quantification as compared to its gamma camera counterpart, SPECT [10].

Of all the PET tracers, ^{18}F-FDG is still the most important and commonly used. Along with its use in oncology, ^{18}F-FDG is being increasingly being used in cardiology, neurology, infections, and rheumatological indications. As a glucose surrogate, FDG targets the glycolytic pathway for intracellular sequestration and shows increased uptake by malignant cells and active inflammatory cells. This is the principle of ^{18}F-FDG/PET imaging [11]. Other than ^{18}F-FDG, other commonly used PET tracers are 18F-sodium fluoride (F18 NaF) for evaluation of bone metastasis, N13 ammonia and Rb82 for myocardial blood flow evaluation, and Ga-68-labeled receptor imaging in carcinoma prostate and neuroendocrine tumors (NETs) [12].

4 Radiommunodiagnostics

Radioimmunodiagnostics is the use of radiolabeled monoclonal antibodies for diagnostic imaging. It is used in diagnosis, assessing treatment response, and to select suitable patients for immunotherapy and targeted drug delivery. It depicts the heterogeneity of the primary tumor and metastatic sites and predicts the response to therapy. Common targets are CD20, CD44, epidermal growth factor receptor (EGFR), vascular epidermal growth factor receptor (VEGFR), human epidermal growth factor receptor 2/neu (HER2/neu), and prostate-specific membrane antigen (PSMA) [13]. Commonly used radioisotopes are zirconium-89 (Zr-89), copper-64 (Cu-64), and iodine-124 (I-124). Previously, the whole of monoclonal antibodies were used for imaging purposes; however, now there is a move toward the use of antibody fragments with smaller molecular size such as affibodies, diabodies, and nanobodies [14]. These newer agents have faster blood pool clearance and help perform early imaging. Some of the agents with active research interest are listed in Table 4.

Table 4 Radioimmunodiagnostic agents

Radiopharmaceuticals	Target	Tumor
Zr89 bevacizumab	VEGF	Breast cancer, multiple myeloma
Zr89 trastuzumab Cu64 trastuzumab	HER2/neu	Breast cancer
Zr89 cetuximab	EGFR	Colorectal cancer
Cu64 rituximab	CD20	B cell lymphoma
Zr89 PSMA	7E11	Prostate cancer
Zr89 cG250 I124 cG250	CA IX	Renal cell carcinoma

5 Hybrid Imaging

The fusion imaging concept came to the fore in order to combine the functional and anatomical modalities together to get structural and pathophysiological information in the same imaging. Various anatomical imaging modalities like computed tomography (CT) and magnetic resonance imaging (MRI) were considered for fusion with existing functional imaging modalities like SPECT and positron emission tomography (PET). The dual imaging modalities that have been prominently used till date are SPECT/CT, PET/CT, and PET/MRI.

Three-dimensional (3D) reconstructive nuclear medicine imaging techniques have relatively poor resolution. The also provide no anatomical information. On top of that, there can be significant loss of counts during the reconstruction process itself. Thus, image fusion became a necessity to ensure visual quality and quantitative accuracy. Co-registration of anatomical and physiological information has revolutionized molecular imaging by helping differentiate abnormal uptake from physiological uptake. Quantification of tissue uptake and organ functions could also be further improved by correcting the emission data for errors due to photon attenuation, partial volume effect, scatter radiation, etc., using the attenuation correction information obtained from CT [15].

Most SPECT scanners, nowadays, have a dual-headed camera system with an integrated CT scanner. SPECT and CT scans are acquired successively and fused together to create a hybrid image. This hybrid image not only helps localize the uptake to the proper anatomical sites but the CT scan thus obtained can also be used for attenuation and scatter correction of gamma rays. Along with routine diagnostic imaging, new indications of hybrid SPECT scanners are emerging in the field of dosimetry and radiopharmaceutical research. SPECT/CT technology has improved the sensitivity and specificity of gamma camera imaging and has thus reduced the number of indeterminate scans [16].

The first hybrid PET/CT scanner was designed in the late 1990s [17]. Since then, there has been a rapid surge in the commercial implementation of hybrid PET/CT scanners, partly fueled by the increasing interest in diagnostic ^{18}F-FDG whole-body cancer studies. The cross-sectional CT component helps identify the precise anatomical location of FDG-avid areas. Furthermore, the CT attenuation map generated can be used to correct the PET attenuation caused by different tissues. In many cancers, such as lymphomas and malignant melanomas, carcinoma lung PET/CT has become indispensable to staging and response assessment and its use has been adopted into clinical guidelines. There are many clinical situations where MRI is the investigation of choice and provides better anatomical information than does CT scanning. PET can complement the MRI findings with more functional information. However, integrating PET or SPECT is challenging. With recent technological advancements, commercial hybrid PET/MRI systems have come into the market [18]. However, cost is an important factor inhibiting their widespread clinical adoption.

6 Indications of F18-Labeled Radiopharmaceuticals in Clinical Oncology

6.1 ^{18}F-FDG

^{18}F-FDG is the principle oncological tracer. F18 has a half-life of 110 min. It is produced in the cyclotron by ^{18}O (p,n) 18F nuclear reaction using $H_2{}^{18}O$ as the target. ^{18}F-FDG is an analogue of glucose and gets metabolically trapped as FDG-6-phosphate inside tumor cells. Tumor cells alter their metabolism to selectively increase energy generation via the glycolytic pathway [19]. This phenomenon is known as the Warburg effect. The clinical uses of ^{18}F-FDG PET/CT have increased immensely in the past two decades [20, 21]. Indications of ^{18}F-FDG PET/CT in oncology can be summarized in the following points:

1. Initial staging in patients with a known malignancy
2. Monitoring response to therapy excluding residual disease
3. Restaging in the setting of relapse
4. Identification of the primary tumor in the presence of a metastatic lesion
5. Localizing occult disease in patients with an elevated tumor marker
6. Guiding special clinical strategies such as radiotherapy planning and directed biopsy
7. Evaluating an indeterminate lesion detected by anatomical imaging to differentiate benign from malignant
8. After treatment completion as a follow-up investigation

6.1.1 The Role of FDG PET/CT in Specific Tumors

Lymphomas

^{18}F-FDG PET/CT has become indispensable to staging, assessing response to treatment, and restaging of FDG-avid lymphomas [22]. It is performed at the initial evaluation stages in about 30% cases [23]. It has excellent sensitivity in picking up both the nodal and extranodal disease sites (Fig. 1). FDG scores over marrow biopsy in detecting lymphomatous marrow lesions in Hodgkin's lymphoma and is considered equal to marrow biopsy in non-Hodgkin's lymphoma [24]. The Deauville five-point scale is used for evaluating the response at interim or at the end of the treatment. Interim ^{18}F-FDG PET/CT performed for response assessment has emerged as an important tool for prognosis. New evidence has emerged in Hodgkin's lymphoma in favor of using interim PET/CT for response-adapted treatment [25].

Lung Cancers

^{18}F-FDG PET/CT with contrast is now widely used to stage the primary lesion and regional lymph nodes. In addition, it is an excellent tool to detect distant metastases, except brain metastases (Fig. 2). ^{18}F-FDG PET/CT is recommended by the National Comprehensive Cancer Network (NCCN) as a standard diagnostic procedure in the pretreatment evaluation of all operable lung cancers [26]. It is a useful adjunct in the characterization of indeterminate solitary pulmonary nodules and pretreatment staging of lung cancer with additional information about the primary tumor, mediastinal nodal status, and remote metastases when compared to a conventional modality like CT [27]. ^{18}F-FDG PET/CT and MRI brain have become the standard staging workups worldwide [28]. They also play a role in guiding the proper biopsy site, radiotherapy planning, response assessment, and restaging. The potential of ^{18}F-FDG PET/CT to provide information about

Fig. 1 Baseline and interim (four cycles) F18 FDG PET/CT of a 32-year-old man with a diffuse large B-cell lymphoma. Maximum intensity projection (MIP) and fused transaxial images are shown. Baseline MIP (**a**) showing cervical nodes (line arrow), abdominal nodes (block arrow), bowel thickening (arrow head), and inguinal nodes (double arrow). Baseline transaxial (**b**) showing cervical nodes (**c**) and bowel wall thickening. Interim MIP (**d**) and transaxial (**e** and **f**) images showing complete regression of nodes and bowel wall thickening

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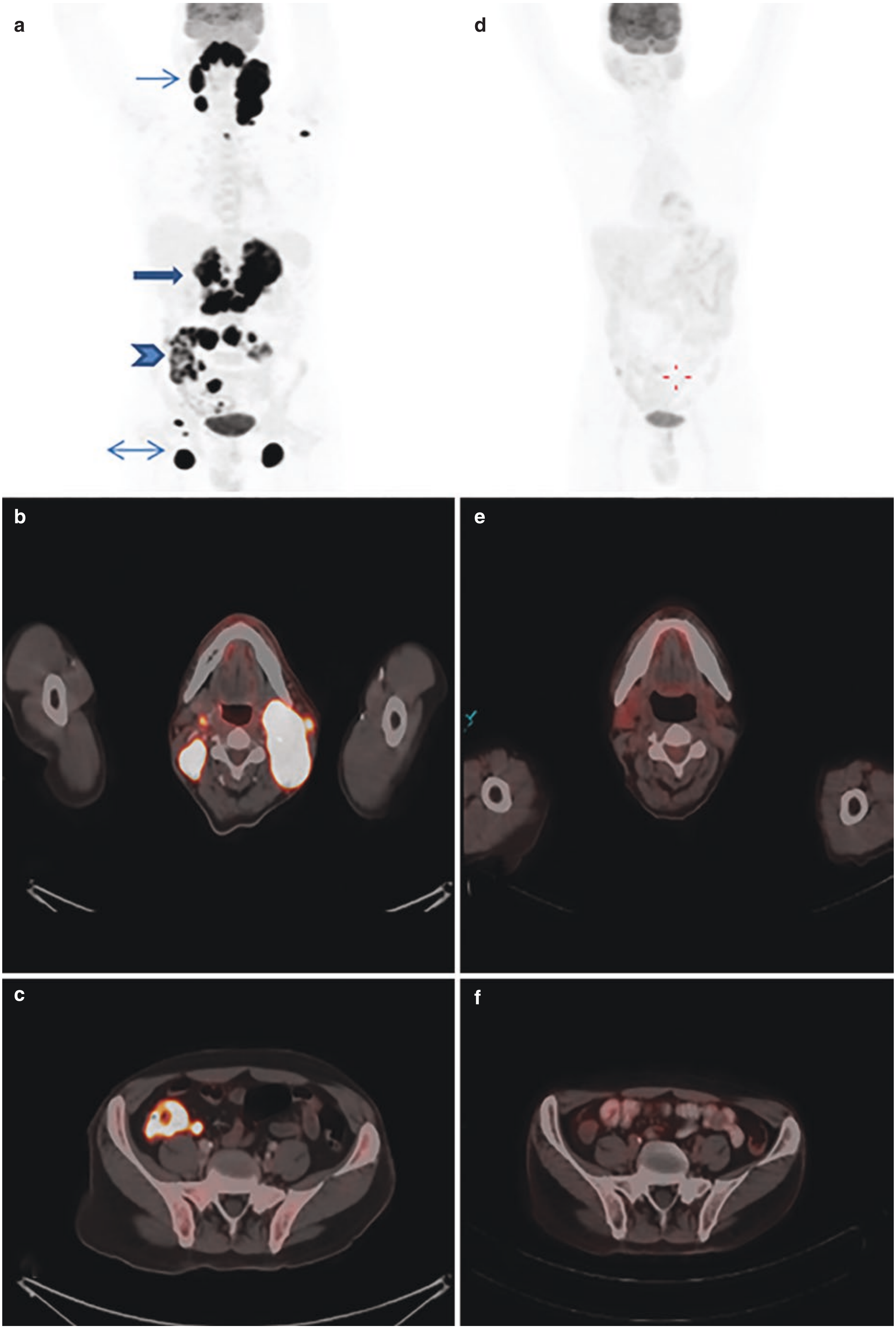
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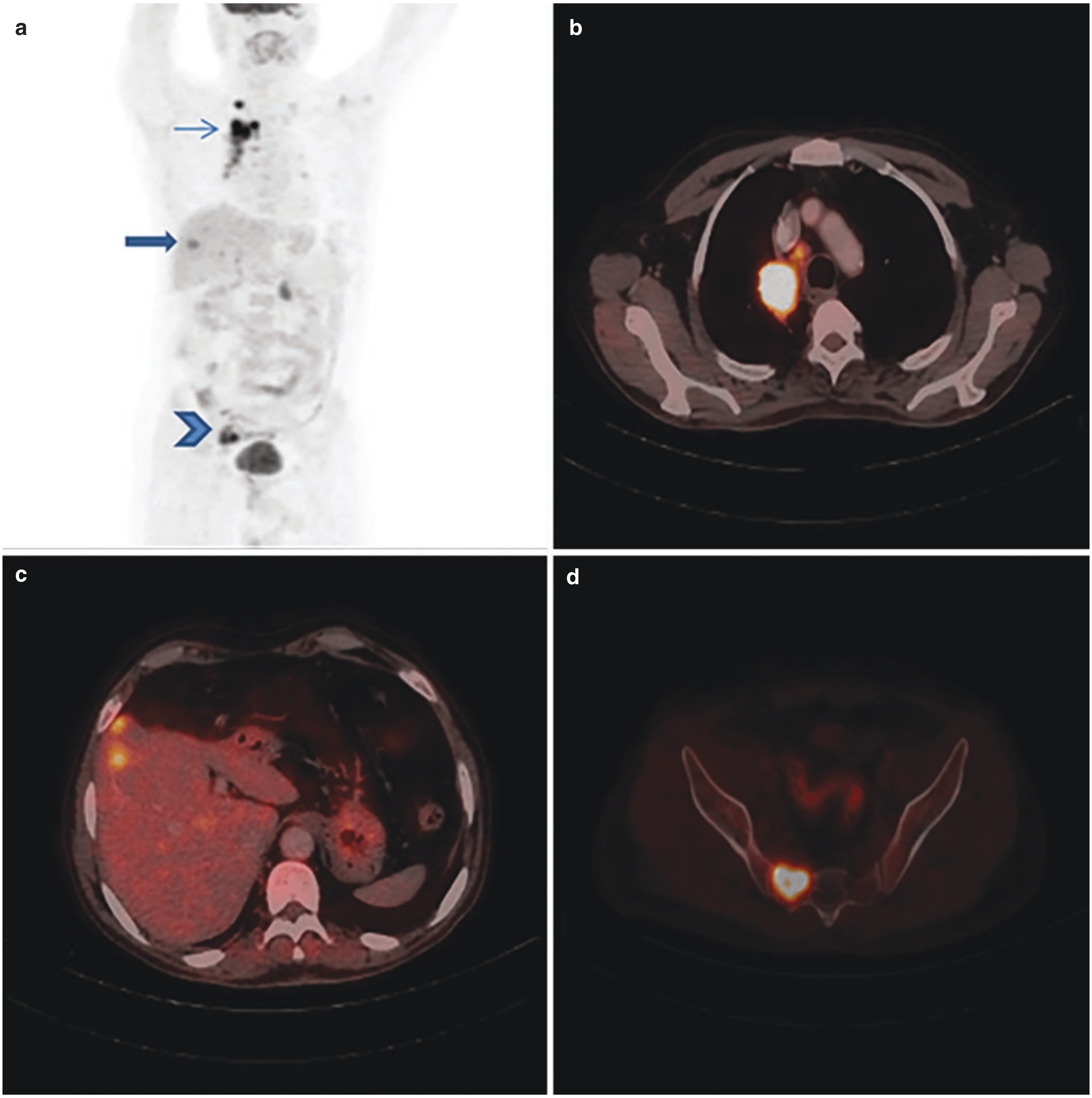

Fig. 2 Baseline F18 FDG PET/CT images of a 55-year-old man with carcinoma of the right lung. Maximum intensity projection (MIP) and fused transaxial images are shown. MIP (**a**) showing lung primary with mediastinal nodes (line arrow), liver metastases (block arrow), and skeletal metastases (arrowhead). Transaxial images showing (**b**) primary lung lesion with mediastinal nodes, (**c**) liver metastases, and (**d**) skeletal metastases in the sacrum

the metabolism of a tumor has been used to prognosticate patients.

Esophageal Carcinoma

For primary tumor (T) staging, PET/CT is inferior to endoscopic ultrasound to accurately measure the depth of invasion. ^{18}F-FDG PET/CT scores highly in detecting nodal and distant metastases and outperforms conventional imaging. PET/CT has extremely high sensitivity and specificity of 96% and 95%, respectively, for detecting nodal disease [29]. PET/CT scores over other modalities in detecting distant metastasis and prevents unnecessary surgical explorations by detection of metastatic disease. In approximately 40% of patients, PET/CT changes clinical management [30, 31]. It also helps in assessing response to neoadjuvant chemotherapy and concurrent chemoradiation by excluding residual disease.

Bone and Soft Tissue Tumors

^{18}F-FDG PET/CT has an important role in the staging of high-grade sarcomas. In Ewing sarcoma, PET/CT has outperformed conventional modalities in staging and detecting early recurrence [32]. It has also shown usefulness in the detection of the primary tumor and metastases in other sarcomas like osteosarcoma and rhabdomyosarcoma [33]. In addition, PET/CT is now used for assessing response to neoadjuvant chemotherapy in sarcomas. PET/CT can also demonstrate areas of sarcomatous changes in benign chondroid tumors by identifying the hypermetabolic focus [34].

Head and Neck Malignancies

PET/CT has high diagnostic accuracy in detecting nodal and distant metastases in head and neck primary tumors as well as sites of the second primary. Early detection of distant metastases can change the treatment plan accordingly. PET/CT has a high negative predictive value of almost 100% for distant metastases [35]. It is used for response assessment after chemoradiotherapy and is recommended after 8–12 of treatment completion to avoid false-positive inflammatory FDG uptake. It has a high negative predictive value in posttreatment evaluation to rule out residual or recurrent disease [36].

Breast Carcinomas

PET/CT scores highly in ruling out distant metastasis in cases of locally advanced breast carcinoma. It is also used in evaluating indeterminate lesions detected on conventional staging modalities like CT or bone scanning. FDG PET/CT has a questionable role in the detection of axillary nodes. However, its sensitivity for detecting internal mammary nodes is high. It can also predict the outcome after neoadjuvant chemotherapy [37, 38].

Melanomas

FDG PET/CT is the best modality to evaluate nodal and distant metastases in advanced cutaneous melanomas [39]. It is also widely used for detecting metastases from mucocutaneous melanomas in the anorectum and head and neck region.

Cancer of Unknown Primary

Early detection of cancer of unknown primary is important for avoiding unnecessary investigations and starting tumor-specific therapy. FDG PET/CT plays a role in detecting cancer of unknown primary in about 30–50% of cases [40].

Colorectal Carcinomas

PET/CT is often used as a second-line imaging tool in the initial staging of colorectal malignancies. It helps in better characterization of indeterminate liver lesions and is used in evaluating extrahepatic disease before the surgical resection or ablation of liver metastases [41]. PET/CT has an important role in the evaluation of recurrent colorectal carcinomas presenting with rising carcinoembryonic antigen (CEA) levels with a sensitivity of more than 94% for detecting recurrence [42].

Apart from this, PET/CT has an obvious role in tumors like gastrointestinal stromal tumors (GISTs), gall bladder and biliary tract malignancies, poorly differentiated carcinomas of the thyroid, malignant mesotheliomas, cervical cancers, urothelial carcinomas, germ cell tumors of the testis, poorly differentiated neuroendocrine tumors, etc. Evidence of FDG PET/CT in many indications is still emerging and is bound to become more defined with continuing research.

6.2 F18 NaF

^{18}F-sodium fluoride is a PET-based bone scan tracer. F18 fluoride localizes to areas of active bone turnover by chemical adsorption [43]. It clears from the blood faster than the other popular bone-seeking radiopharmaceutical, methylene diphosphonate (MDP). The uptake of F18 NaF is dependent on blood flow and bone remodeling. PET technology also offers better resolution than does planar imaging, and, when performed as a part of hybrid PET/CT imaging, CT allows better morphological characterization of the lesion. The most important indication of F18 NaF in oncology is to detect and characterize metastatic bone lesions (Fig. 3). Other indications where F18 NaF is useful in oncology are to determine the viability of bone graft and also the areas of increased osteoblastic activity as a prelude to bone pain palliation therapy with radiopharmaceuticals [44].

6.3 ^{18}F FLT (3′-Deoxy-3′-^{18}F Fluorothymidine)

This is a surrogate of nitrogen base in DNA strands. It enters a cell by active transport and is trapped after undergoing phosphorylation by thymidine kinase 1. Unlike thymidine, F18 fluorothymidine cannot be incorporated into DNA strands and gets trapped inside the cell. F18 FLT uptake is a marker of thymidine kinase 1 expression and thus cellular proliferation [45]. Various studies have shown that there is a strong correlation between the proliferation marker “Ki-67” detected in histopathology and F18 FLT uptake [46]. Studies have shown that FLT has an important role in grading gliomas and detecting recurrence. One disadvantage of F18 FLT is that it does not cross the blood–brain barrier and so it will not be concentrated by low-grade gliomas where the blood–brain barrier stays intact [47]. It has shown promise in guiding and planning of radiotherapy and assessing treatment response.

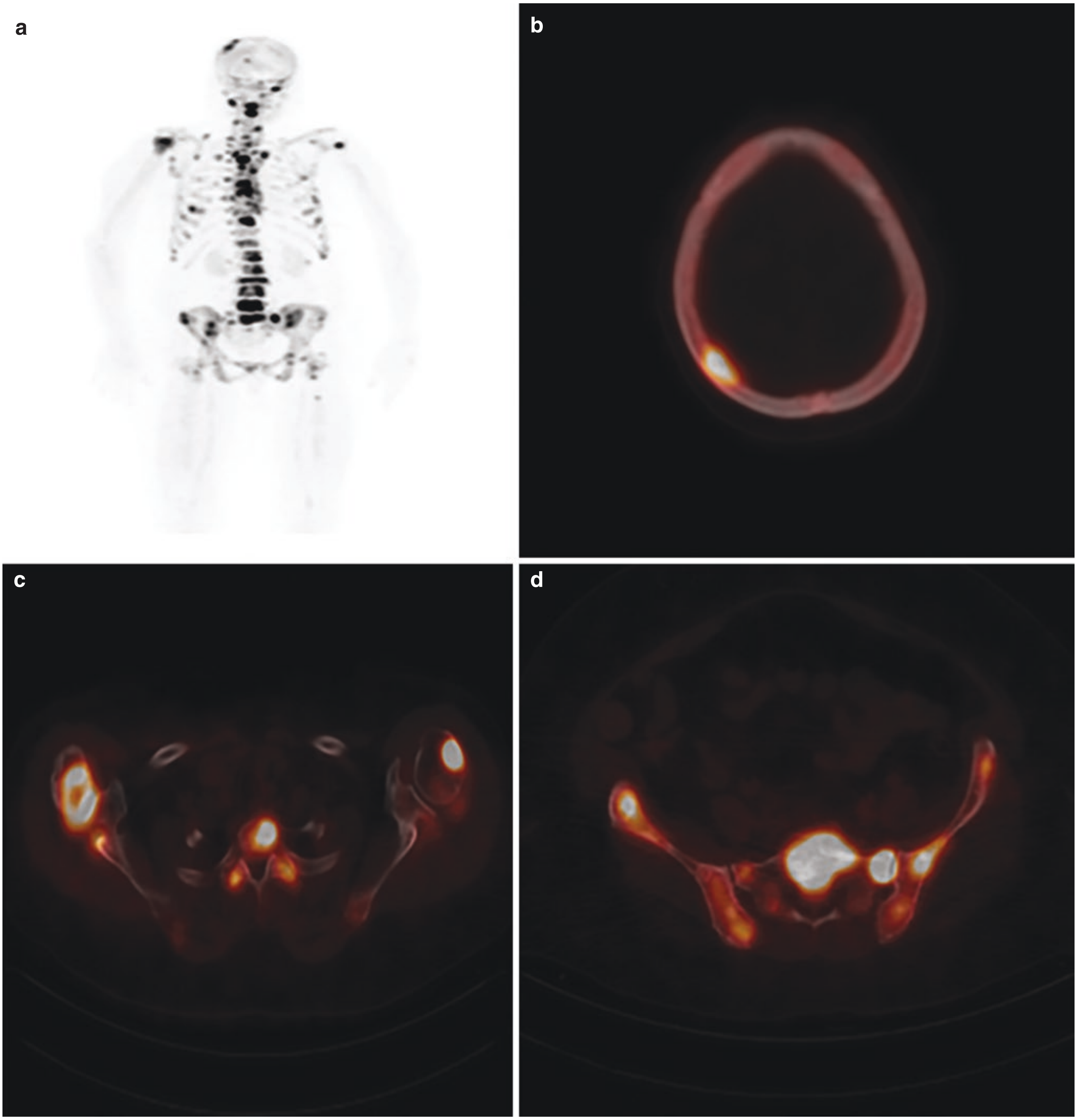

Fig. 3 F18 NaF PET/CT images of a 44-year-old woman with locally advanced carcinoma of the left breast. Maximum intensity projection (MIP) and fused transaxial images are shown. MIP (**a**) showing extensive skeletal metastases involving the axial and appendicular skeletal system. Transaxial images showing metastases in (**b**) the skull, (**c**) bilateral humeri, dorsal vertebra, and (**d**) sacrum and bilateral iliac bone

6.4 F18 FMISO (F18 Fluoromisonidazole)

This is an imaging agent for hypoxia. This particular molecule has a $–NO_2$ functional group. In the absence of oxygen, this group is reduced by accepting an electron in the anionic form of $R\text{-}NO_2$. If reduced, then this moiety becomes an alkylating amine ($R\text{-}NH_2$) compound and is retained in the cell, thus getting trapped effectively [48]. Uptake of F18 FMISO in a tumor depends on the degree of hypoxia and the biology of the tumor. Hypoxia makes cancer cells more resistant to radiation and a number of chemotherapeutic agents. The level of hypoxia in a tumor is also an important prognostic marker [49]. Locating hypoxic regions in a solid tumor will thus help in proper therapy planning. F18 FMISO

PET/CT imaging has been used for localizing hypoxic sites and then using these images for radiation treatment planning. Several studies have demonstrated that hypoxia and FMISO uptake in variety of solid tumors like glioblastoma multiforme, lung cancer, cervical cancer, head and neck cancer, and breast cancer correlates with tumor prognosis [50].

6.5 ^{18}F FET (^{18}F-Fluoro-ethyl-tyrosine)

This is an amino acid tracer that can enter the brain parenchyma through an intact blood–brain barrier using the L-type amino acid transporter 1 (LAT1). This unique mechanism of localization has made this a highly lucrative tracer for imaging gliomas [51]. Unlike FLT, it shows localization in low-grade gliomas as well. It can also help differentiate between low-grade and high-grade gliomas. In high-grade gliomas, there is rapid uptake and washout, and, in low-grade gliomas, there is gradual accumulation of the tracer. These uptake patterns can be easily discerned by performing a dynamic study and plotting a time–activity curve or by carrying out multiple static images at different time points. Apart from grading gliomas, F18 FET also helps in diagnosing recurrence, evaluating treatment response, and planning radiotherapy. Studies have been conducted to evaluate the role of F18 FET in prostate cancer, meningioma, and pediatric lymphomas [52].

7 Radioguided Surgery and Radioguided Biopsy

The sentinel lymph node (SLN) biopsy is the most popular radioguided technique. It increases the identification rate of occult lymphatic metastases and also obviates the need of blind lymph node biopsies. Lymphoscintigraphy prior to surgery helps map out the drainage patterns to guide the surgeon toward the sentinels. An intratumoral or peritumoral injection of technetium-99m sulfur colloid is performed, guided by ultrasound or computed tomography, up to 24–36 h prior to surgery [53]. Intraoperative “hot” node detection is then carried out with the help of a gamma probe. Due to better special resolution and having a cross-sectional imaging component, SPECT/CT improves SLN detection. This technique of radioguided biopsy is being used in head and neck cancers, breast cancer, penile carcinoma, malignant cutaneous melanoma, and carcinoma of the cervix [54]. Another radioguided procedure in surgical oncology is resection of the parathyroid adenoma. Parathyroid scintigraphy can be used not only to localize parathyroid adenoma but also to help determine whether the surgery is successful [55].

Radioguided biopsy has been gaining much popularity in recent years as FDG PET/CT modality has become more ubiquitous. FDG PET helps identify the most metabolically active lesions and also helps guide the biopsy site by decreasing nondiagnostic sampling. A PET-guided biopsy can be performed in two different ways: the first one is to obtain a PET scan separately and then to fuse it with the CT image/MRI image of the guided biopsy procedure. Alternatively, a real-time PET/CT scan can be performed and a biopsy can be obtained simultaneously, thus saving time. In real-time imaging, single-bed PET/CT is performed to confirm the biopsy site and the biopsy is collected. Most commonly, it is used for diagnosis of lymphomas, carcinomas of the lungs, bone, liver, and soft tissue lesions [56, 57]. Increased cost and increased radiation exposure preclude the widespread availability of this procedure.

7.1 PET/MRI Hybrid Imaging

Both positron emission imaging and magnetic resonance imaging are well-established diagnostic tools that have been in use for more than 30 years. With the advent of PET/CT hybrid imaging, a new era of diagnostic imaging has begun. This increasing focus on the fusion of anatomical and functional data has led to rapid growth in PET/CT technology and application. However, there are many clinical conditions where CT does not provide adequate morphological information but MRI does. This has led to the development of hybrid PET/MRI systems [58]. The usual workflow of PET/MRI is an integrated system in which PET detector rings are placed inside the MRI gantry. The integrated design allows simultaneous PET and MRI with reduced scanning time and improved registration in the fusion images [59].

In spite of the theoretical promise, there are many unique challenges specific to PET/MRI systems that preclude their widespread use. Most of these are technical issues inherent to the PET/MRI system [60]. The PET components of the system should be devoid of any ferromagnetic substance; this poses a great challenge to designing systems. However, the most pressing challenge comes in the form of attenuation correction [61]. Without a transmission CT scan to generate a linear attenuation coefficient map for attenuation correction, other techniques have to be employed for that. Many different techniques have been used, such as using special MRI sequences for attenuation correction, using predefined attenuation maps, etc., to address this issue [62].

In spite of the challenges, there are many distinct advantages offered by a PET/MRI system over a PET/CT: it improves lesion detection in the brain, kidneys, liver, breast, and bone; it improves T staging of solid tumors by providing better soft tissue delineation; and it comparatively decreases radiation exposure to the patient and improves motion correction.

7.1.1 Specific Indications of PET/MRI in Clinical Oncology

Head and Neck Cancers

PET/CT is a well-established modality of choice for staging head and neck malignancies; its most important indication is in nodal staging and evaluation of distant metastasis. Most of the T staging can be effectively performed by clinical methods and endoscopic examinations. However, in few locations such as the pyriform sinus, floor of the mouth, and base of the tongue, it becomes difficult to evaluate T staging by only using clinical methods. Owing to excellent soft tissue discrimination, MRI is a magnificent tool for evaluation of lesion extent and local invasion. In this regard, PET/CT can be limiting. PET/MRI fusion thus provides better "T" and "M" staging in head and neck malignancies in a single imaging modality. However, concrete evidence-based data in this regard are lacking. Most literature published are small case series [62].

Liver Metastasis

Identifying liver metastasis is extremely important in various cancers. PET/CT is a common modality to assess liver metastasis. However, MRI has higher sensitivity and accuracy as compared to PET/CT [63]. It provides a better detection rate and diagnostic confidence, especially for metastasis of <1 cm size [64].

Brain Tumors

MRI provides excellent morphological information of brain pathologies. MRI/PET can better grade gliomas, provide better information regarding spread of the tumor along the white matter tracts, and is better for treatment response evaluation, as compared to PET/CT [65].

Prostate Cancer

PET/MRI may help in the precise mapping of a PET-positive lesion and scores over PET/CT in excellent anatomical localization of the lesion [66]. Carbon-11 (C-11) choline PET/MRI in 32 patients with prostate cancer showed better anatomical delineation of the lesions to the bone and pelvic organs or tissues by C-11 choline PET/MRI as compared with C-11 choline PET/CT [67].

Lung Cancer

PET/MRI has proven advantageous in T staging in cases of mediastinal involvement and chest wall infiltration [68]. It can be used as a one-stop imaging for evaluating brain metastasis during staging.

Breast Cancer

PET/MRI helps in evaluating the primary lesion and to look for distant metastasis. It scores over PET/CT in evaluating liver and brain metastases [69].

Bone and Soft Tissue Malignancies

It helps in identifying marrow-infiltrating lesions in sarcoma and multiple myeloma. It also helps in staging of the primary tumor [70].

Pediatric Malignancies and Lymphomas

It offers lower radiation exposure as compared to PET/CT. Special MRI sequences like diffusion-weighted imaging (DWI) help in detecting highly cellular lesions, and can thus act complementary to FDG/PET [71].

8 Therapeutic Nuclear Medicine in Oncology Practice

8.1 The Fundamental Principles of Radionuclide Therapy Using Unsealed Sources

In contrast to gamma rays utilized in diagnostic imaging, particulate ionizing radiations such as α, β, and auger electrons are used for therapeutic purposes in clinical oncology to delivery highly selective radiation doses to the diseased sites. Hence, this could be considered the fundamental difference between the radiopharmaceuticals tagged with a therapeutic radioisotope and those used for diagnostic purposes. Some of the commonly used therapeutic radionuclides with their physical characteristics are enlisted in Table 5.

Table 5 Therapeutic radionuclides

	I-131	P-32	Sm-153	Sr-89	^{177}Lu
Eβmax (MeV)	0.606	1.71	0.81	1.46	0.497
Eβmean (MeV)	0.190	0.70	0.23	0.58	0.165
Soft tissue range	0.6–2 mm	3 mm	0.6 mm	2.5	<1.5 mm
γ-Rays	364 keV (80%)	No	103 keV (28%)	910 keV (0.01%)	113 keV (6.6%), 208 keV (11%)
Half-life	8.02 days	14.3 days	1.9 days	50.5 days	6.7 days
Route of administration	Oral	Oral	IV	IV	Intravenous

9 Specific Indications in Clinical Oncology

9.1 Thyroid Cancer

Radioactive iodine (RAI) has been used over the last six decades in patients with differentiated thyroid cancer (DTC) in the post-total thyroidectomy setting. The reason for this is that follicular cells of the thyroid have sodium iodide symporters (NISs) that transport iodine with Na^+ across the basolateral membrane [72]. A human NIS is a glycoprotein containing 643 amino acids. The gene is located on chromosome 11. Well-differentiated thyroid cancer cells usually express NISs and, as a result, are able to concentrate RAI, thus enabling the use of RAI for ablative purposes [73]. Studies have shown that postoperative RAI use significantly improved disease-free survival (DFS) in patients with DTC [74]. RAI is administered to post-thyroidectomy patients with differentiated thyroid cancer. The indications for RAI administration can be one of the following: (1) remnant ablation, (2) adjuvant treatment, and (3) therapy of the metastatic disease.

9.1.1 Remnant Ablation

RAI is an effective modality in ablating remnant thyroid tissue in a postoperative bed as well as in destroying microscopic disease present in a post-thyroidectomy DTC patient. The rationale behind is to effectively use serum thyroglobulin as a tumor marker and detect disease recurrence. No standard definition of a successful ablation is available. Most groups, however, consider successful remnant ablation as no appreciable uptake in the thyroid bed in a diagnostic scan at 6–8 months after the therapy or, if appreciable, a percentage uptake <0.1% and/or a stimulated serum thyroglobulin (Tg) concentration <1 ng/mL [75]. The dose of RAI for remnant ablation has been a controversial issue. However, now, most authorities agree that a dose of 30–50 mCi of RAI is sufficient for successful remnant ablation [76]. The target for remnant ablation is usually low-risk patients. However, the latest guidelines by the American Thyroid Association (ATA) have questioned the need for remnant ablation in low-risk patients [77].

9.1.2 Adjuvant Therapy

By definition, adjuvant therapy is administered when there is a suspicion of residual microscopic disease being left out during surgery, or there is tumor spillage during surgery, to decrease the risk of future recurrence and improve disease-free survival. DTC patients with intermediate-risk features, such as locoregional nodal metastasis, tumor with extrathyroidal extension, or tumor with vascular invasion or with high-risk histology, are usually considered for adjuvant therapy. Adjuvant RAI therapy is associated with increased survival for intermediate-risk papillary thyroid cancer [78]. The usual dose of RAI for adjuvant therapy is 150 mCi [77].

9.1.3 Treatment of Metastatic Diseases

RAI is the treatment of choice for iodine-avid metastatic thyroid cancer. The most frequent sites of metastasis are the lungs and bones. Pulmonary micrometastasis responds extremely well to RAI treatment and should be treated every 6–12 months until complete resolution [79, 80]. The dose is 100–200 mCi or 100–150 mCi for patients aged 70 years or more. Bone metastasis can never be cured with RAI but significantly increases progression-free survival. RAI activity up to 200 mCi can be empirically administered [81] (Fig. 4).

9.1.4 Treatment for Iodine Refractory Thyroid Cancer

Iodine refractory metastatic thyroid cancer poses a unique therapeutic challenge to the clinician. The most accepted mode of treatment for these patients is by tyrosine kinase inhibitors [20]. However, these treatments carry several serious side effects. In this regard, somatostatin receptor (SSTR) expression in these patients and subsequent treatment with Lu-177-tagged peptide receptor radionuclide therapy (PRRT) have been explored in various case series and studies [82, 83], though, in our experience, high uptake to justify PRRT occurs in 15–20% of such patients.

9.2 Polycythemia Rubra Vera

Polycythemia rubra vera is a slow-growing tumor of the bone marrow erythroid lineage. The radionuclide traditionally used in this setting is the reactor-produced phosphorus-32. P-32 is a pure β-emitting radionuclide with a physical half-life of 14.3 days. The biological half-life of P-32 in the bone marrow is 7–9 days. The usual dose in polycythemia vera is 2–3 mCi/m^2 (5 mCi) or higher, i.e., 0.1 mCi/kg (max 7 mCi). P-32 gets incorporated into nucleic acids of rapidly proliferating cells, resulting in suppression of their growth. The patient is pretreated with venesection till hematocrit <42–47% and chemotherapy is usually discontinued for 1 week [84].

9.3 Bone Pain Palliation

There are many radiopharmaceuticals used for pain palliation in metastatic bone disease. Most of these radiopharma-

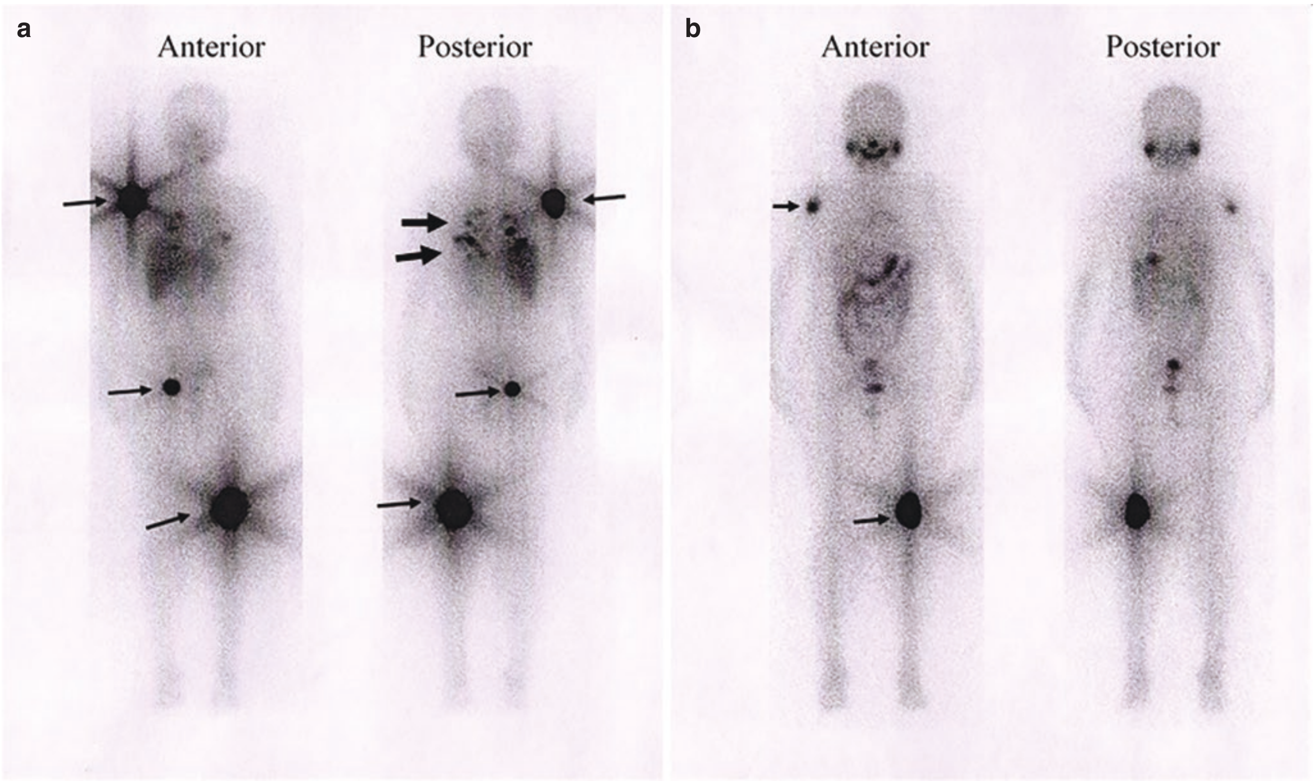

Fig. 4 A 31-year-old lady with a metastatic follicular variant of papillary thyroid carcinoma was treated with 205-mCi iodine-131. A post-therapy whole-body scan (image **a**) showed multiple sites of skeletal metastasis (thin arrows) and bilateral lung metastasis (bold arrows). A follow-up whole-body scan with 3-mCi iodine-131 performed after 1 year showed persistent uptake in the bones (arrows in image **b**). The patient was retreated with 200 mCi of RAI

ceuticals get incorporated into hydroxyapatite crystals and areas of high bone turnover, especially osteoblastic metastasis, and irradiate the area with β-radiation to alleviate pain. Some such agents are Sr-89 chloride, Sm-153 lexidronam, P-32-oral, and Re-186 etidronate [85]. In an Indian setting, Sm-153 EDTMP and Lu-177 EDTMP are the common radiopharmaceuticals used for this purpose in view of their easy availability through indigenous production.

9.4 Neuroblastomas

I-131-labeled MIBG is usually used as a diagnostic and staging agent for stage III/IV metastatic neuroblastoma (Fig. 5). Since I-131 is a β-emitter, this particular compound can be used for therapeutic purposes in metastatic and inoperable cases of a neuroblastoma. MIBG is a alkyl guanidine and a noradrenaline and guanethidine analogue. After intravenous (IV) administration, ^{131}I-MIBG is selectively concentrated in adrenergic innervations. It is taken up by the neuronal uptake 1 mechanism and stored in neurosecretory granules (adenosine triphosphate (ATP)-dependent process). Typical indications for I-131 MIBG therapy in neuroblastoma are metastatic MIBG-avid disease and unresectable tumor. The usual dosage of MIBG is 100–200 mCi, which is reduced in impaired renal function and myelosuppression. The specific activity of I-131 in ^{131}I-MIBG used for therapy should be 1.48 GBq/mg [86, 87].

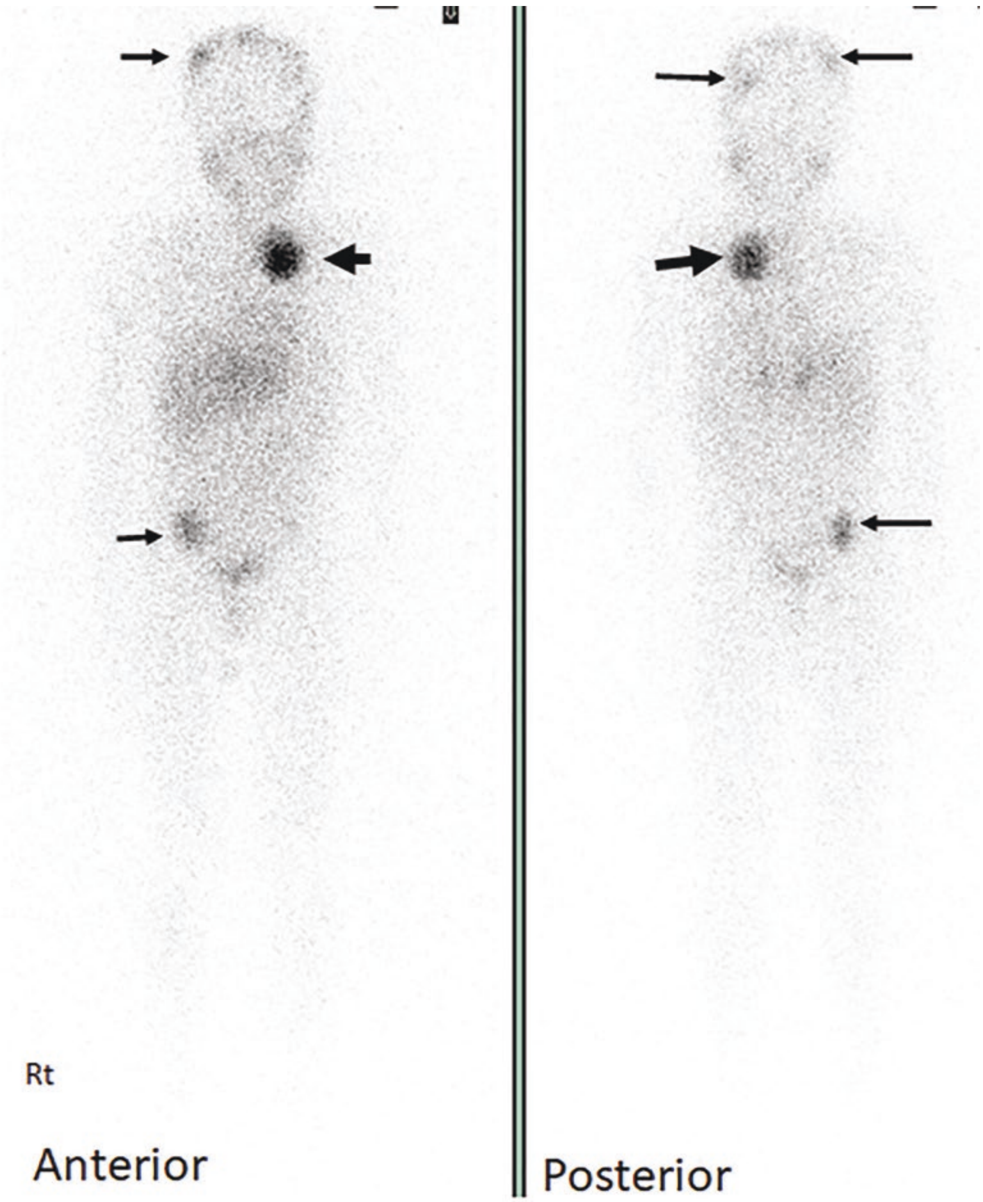

Fig. 5 A planar MIBG scan of a 7-year-old child with mediastinal neuroblastoma showing MIBG-concentrating lesion in the left upper thorax (bold arrow) and metastatic bone lesions in the skull and pelvis (thin arrows)

10 Theranostics

The term “theranostics” literally means coupling of therapy and diagnostics. The theranostic approach pairs diagnostic imaging and therapy using the same or similar molecule with different radiolabeling [88]. Sometimes in theranostics, the same molecule is administered at different dosages for diagnostic and therapeutic indications. Although this term has been used recently, the principle has been in practice for several years. In fact, I-131 can be considered as the first theranostic agent in nuclear medicine history, which was used for therapy and imaging in thyroid diseases. Presently used iodine-131 and lutetium-177 are both γ- and β-emitters, thus making them suitable for both imaging and therapy. Different isotopes of the same element with different characteristic of emission, like iodine-123 (γ-emitter) and iodine-131 (γ- and β-emitters), can also be used for theranostic purposes. The use of theranostic pharmaceuticals has been on the rise. Some of the commonly used theranostic pairs and their clinical uses are summarized in Table 6.

10.1 Receptor-Targeted Therapy in Theranostics

Two recent developments in receptor-targeted therapy have been the classical examples of the theranostic approach that has been used in clinical oncology.

Table 6 Theranostic pairs and their clinical uses

Theranostic molecule	Iodine	MIBG	SSA	PSMA ligands	Benzamide/ arylcarboxamide
Target	Thyroid cancer cells	Neurosecretory granules	SSTRs, especially the subtype SSTR2	PSMA	Melanin
Planar imaging/ SPECT	131I and 123I	$^{[131I]}$I-MIBG, $^{[123I]}$I-MIBG	SSA labeled with indium-111	$^{[123I]}$I-MIP-1072	$^{[123I]}$I-BA52
PET	124I	$^{[124I]}$I-MIBG	[68Ga]-DOTATATE [68Ga]-DOTATOC [68Ga]-DOTANOC	$^{[68Ga]}$PSMA-11 $^{[68Ga]}$PSMA-617	$^{[18F]}$-ICF15002
Therapeutic agent	131I	$^{[131I]}$I-MIBG	[177Lu]-DOTATATE [177Lu]-DOTATOC [90Y]-DOTATOC [90Y]-DOTATATE	$^{[177Lu]}$-J591 $^{[90Y]}$-J591 $^{[131I]}$I-MIP-1095 $^{[177Lu]}$-PSMA-617	$^{[131I]}$I-BA52 $^{[131I]}$I-ICF15002
Indication	Thyroid cancer	Neuroblastomas, pheochromocytomas, paragangliomas, medullary thyroid carcinomas, and other NENs	NENs, especially GEP-NENs	Metastatic prostate cancer	Metastatic melanoma

Table 7 Radiopeptides used for PRRT

	^{90}Y-DOTATOC/ pentetreotide	^{90}Y-DOTA-lanreotide	^{177}Lu-DOTATATE
Type of radiation	β	β	β, γ
Physical T1/2	2.7 days	2.7 days	6.7 days
Chelator	DTPA/DOTA	DOTA	DOTA

10.1.1 Peptide Receptor Radionuclide Therapy (PRRT) in Metastatic Neuroendocrine Tumors (NETs)

This therapy consists of administration of a synthetic somatostatin analogue radiolabeled with a suitable β-emitting radionuclide, which specifically binds to SSTRs (mainly in grade 1–2 NETs) and are internalized thereafter to manifest the therapeutic action [89], thus enabling delivery of a high dose of cytotoxic radiation to tumor cells while sparing the normal tissues. Common radiopeptides used for PRRT are shown in Table 7. Of these, ^{177}lutetium-based radiopeptides are preferred in view of their lesser nephrotoxicity and hematotoxicity compared to the ^{90}yttrium-based radiopeptides owing to the harder β-energy of the latter.

Indication of PRRT:

- SSTR expressing metastatic or inoperable NETs, i.e., well to moderately differentiated midgut NETs [90] and bronchial NETs [91] (Fig. 6)
- Also in medullary thyroid cancer, pheochromocytoma, paragangliomas [92], and neuroblastomas [93]

10.1.2 ^{177}Lu-PSMA Therapy (Peptide Receptor Radioligand Therapy: PRRLT) in Metastatic Castrate-Resistant Prostate Carcinoma

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein receptor expressed on the surface of prostate cancer cells. It consists of 750 amino acids. It acts as an enzyme glutamate carboxypeptidase [94]. It is expressed at low levels in the normal human prostate epithelium. In prostate cancers cells, it is overexpressed almost 1000 times as compared to normal cells. It is expressed in virtually 90–95% of all prostate cancers [38]. The PSMA receptor, after binding to its ligand, undergoes endocytosis and gets internalized into an endosomal compartment inside the cell, which allows PSMA-labeled radioisotopes to be concentrated within the cell [95].

Of all the different PSMA-targeting molecules, small-molecule peptides have had the greatest success, due to their high-binding affinity to the PSMA receptor. This has paved the way for not only better PET imaging agents but also the development of targeted radionuclide therapy for men with prostate cancer. This targeted therapy for prostate cancer has, to date, predominately used lutetium-177 (Lu-177)-labeled PSMA peptides [96]. ^{177}Lu-PSMA is showing promise in the treatment of metastatic castrate-resistant prostate cancer (Fig. 7).

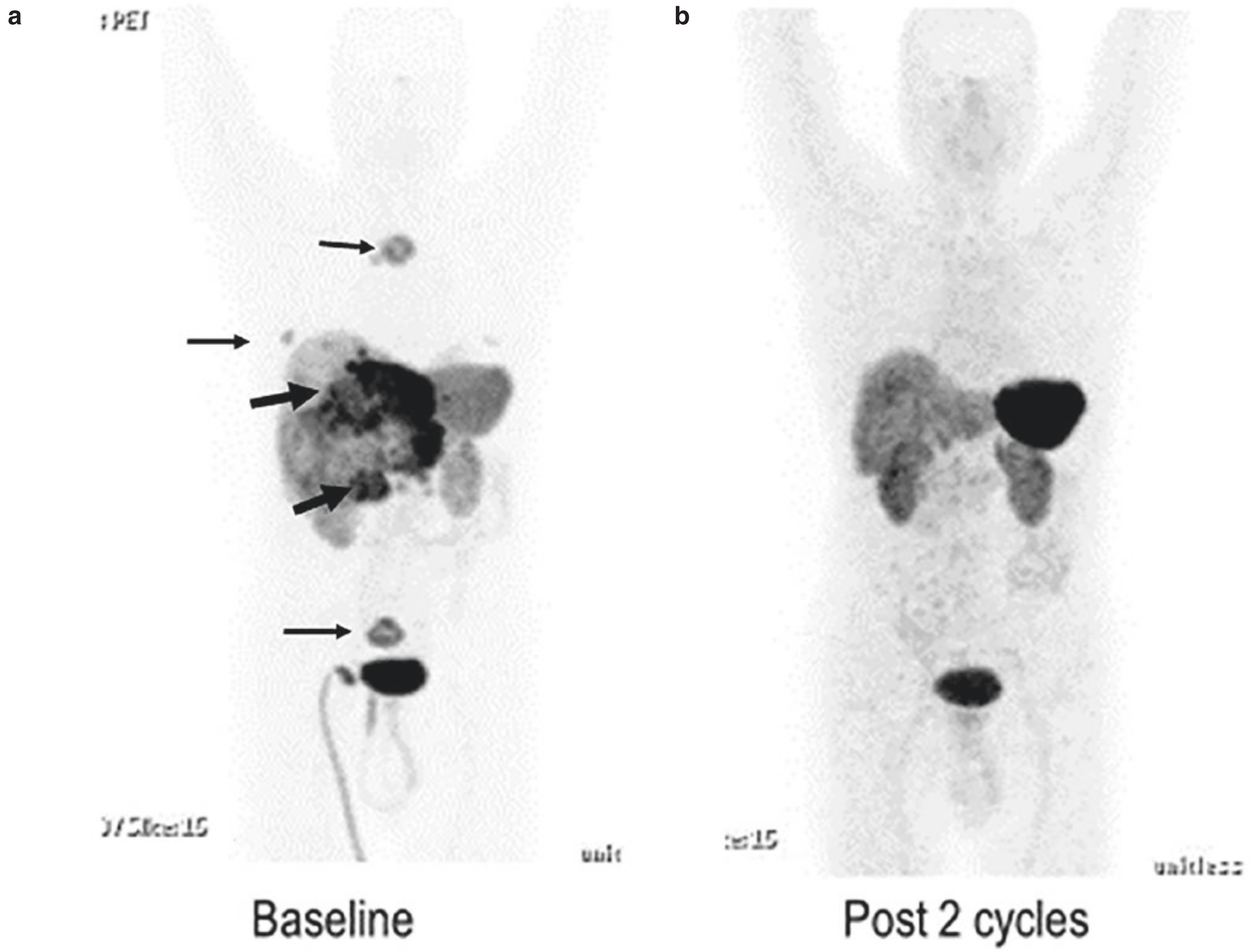

Fig. 6 Ga-68 DOTANOC PET images of a 68-year-old with metastatic grade III neuroendocrine tumor. Baseline maximum intensity projection (MIP) image (image **a**) showing somatostatin receptor expressing metastatic liver lesions, peripancreatic nodes (bold arrows), and skeletal lesions involving the ribs, sternum, and sacrum (thin arrows). MIP of the response assessment scan (image **b**) performed after 2 cycles of Lu-177 DOTATATE (PRRT) and capecitabine + temozolomide combination therapy showing near-complete resolution of the metastatic lesions

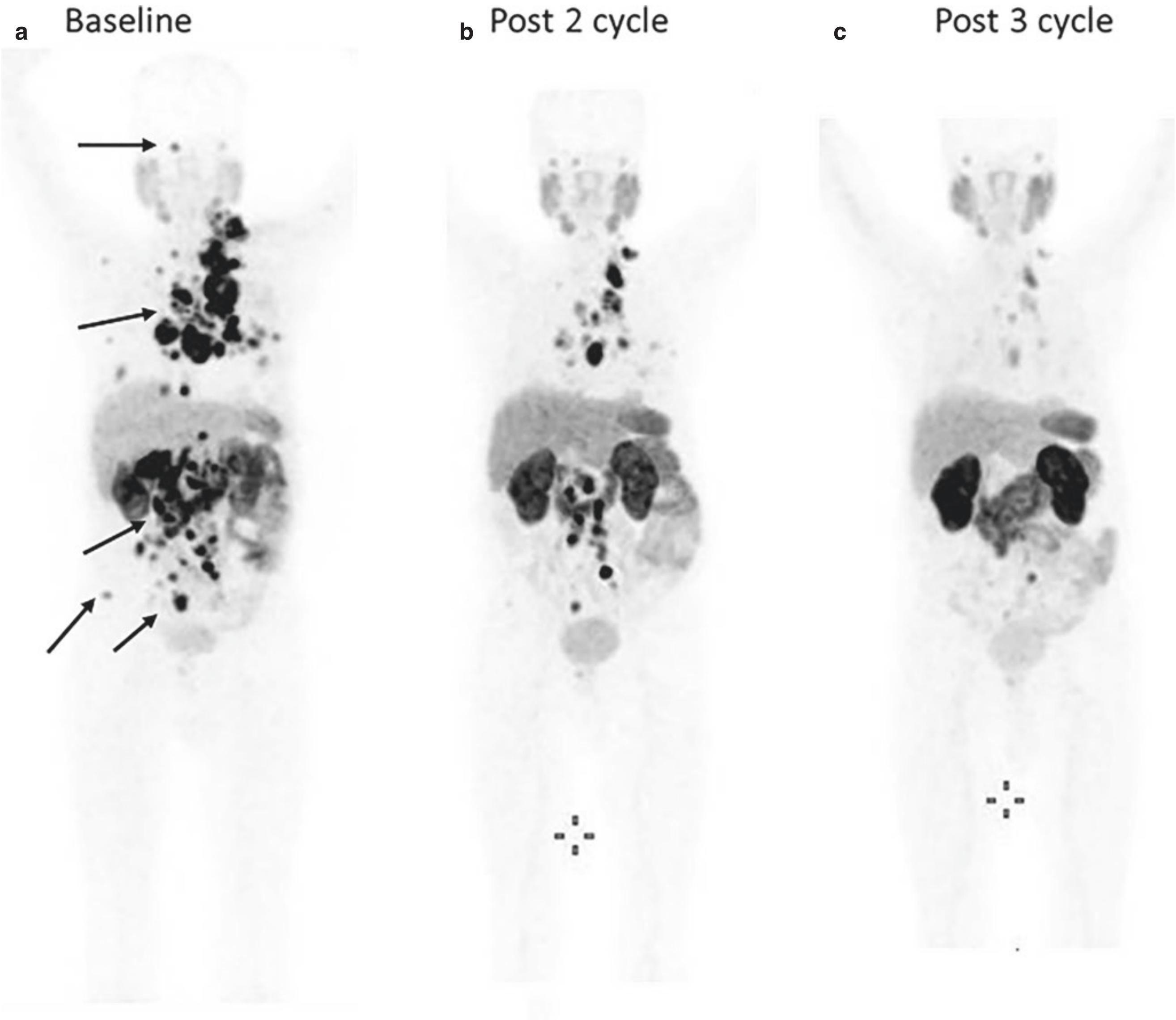

Fig. 7 Serial Ga-68 PSMA PET scan images of a 77-year-old man with metastatic castrate-resistant prostate cancer on Lu-177 PSMA therapy are shown. The baseline MIP image (image **a**) shows extensive nodal and skeletal disease (arrows). Images **b** and **c** showing gradual resolution of the PSMA-concentrating metastatic lesions after successive cycles of Lu-177 PSMA therapy

11 Alpha Therapy

The targeted alpha particle involves administration of a radionuclide, which undergoes alpha decay to treat cancer cells in close proximity. Targets include metastatic prostate carcinoma, leukemias, lymphomas, gliomas, melanomas, and peritoneal carcinomatosis [97]. The main advantages of alpha (α) emitters over the traditional β-emitting radionuclides are their extremely high linear energy transfer (LET), relative biological effectiveness (RBE), and lower intercellular range. Alpha particles are more likely than are β-particles to cause double-strand breaks to DNA molecules, which are harder to mend with DNA repair mechanisms, thus increasing the chance of cell death [97].

11.1 Applications

The following are the major areas where alpha radionuclide therapies have been ventured:

- Metastatic prostate carcinoma: 223-Radium chloride is a Food and Drug Administration (FDA)-approved agent used in castrate resistant prostate cancer (CRPC) with predominantly extensive bone metastases [98]. 225-Ac-PSMA-617 is also under trial for the same, and preliminary data are suggestive of excellent response in bone lesions and soft tissue lesions as well [99].
- Immunotherapy: Antibody agents tagged with 225Ac, 211At, 212Pb, and 213Bi have been tried [100].

- Peritoneal carcinomas: Treatment of peritoneal carcinomas has promising early results using α-emitting agents [100].
- Leukemia: Early trials of ^{225}Ac and ^{213}Bi have shown promise in leukemia patients [100].
- Melanomas: Phase I trials on melanomas with ^{213}Bi have shown promise [100].

12 Radioimmunotherapy

Radioimmunotherapy uses a radioactive isotope (often a β-emitter) chemically bound to a target-specific monoclonal antibody or fragment for cancer therapy. Thus, these radioimmunoconjugates can deliver a high dose of radiotherapy very precisely to the targeted cancer cells expressing the particular antigen [101]. To date, only two radioimmunotherapy molecules have been fully approved by the US FDA for commercial use: ^{90}yttrium ibritumomab tiuxetan (Zevalin) and (131) iodine tositumomab (Bexxar). Both of these compounds target the CD20 antigen expressed on normal and malignant B cells. These are approved for the treatment of refractory indolent B-cell lymphomas. The published literature suggests 20–40% complete response rates and 60–80% overall response rates in these patients. The toxicity profile is typically quite mild [102]. Rituximab has also been tagged with I-131 and Lu-177, and dosimetry data of these molecules have been published.

HER2/neu is overexpressed in approximately 20–25% of breast cancers [103]. HER2-positive breast cancers are known to be aggressive and are associated with poorer prognosis. Lu-177-trastuzumab is being used for specific tumor targeting in HER2-positive breast cancer patients [104].

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Interventional Radiology in Oncology

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Abbreviations

ABC	Aneurysmal bone cyst
CT	Computed tomography
DEB	Drug-eluting beads
DSA	Digital subtraction angiography
DVT	Deep venous thrombosis
EBUS-TBNA	Endobronchial ultrasound-guided transbronchial fine-needle aspiration
GCT	Giant cell tumors
GGO	Ground-glass opacities
HIFU	High-intensity focused ultrasound
IR	Interventional radiology
IRE	Irreversible electroporation
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MWA	Microwave ablation
NSCLC	Nonsmall cell lung cancer
OA	Ophthalmic artery
PE	Pulmonary thromboembolism
PTBD	Percutaneous transhepatic biliary drainage
RFA	Radiofrequency ablation
RILD	Radioembolization-induced liver disease
SEMS	Self-expanding metallic stents
SVC	Superior vena cava obstruction
TACE	Transarterial chemoembolization
TARE	Transarterial radioembolization
TJLB	Transjugular liver biopsy
USG	Ultrasonography

1 Introduction

The term "Interventional Radiology," proposed by Dr. Alexander Margulisin in 1967 as a new subspecialty within the family of imaging sciences, involves the use of image guidance to diagnose and treat diseases in a minimally invasive way. Multiple medical conditions which previously required surgical operative procedures can now be managed in a minimally invasive manner with interventional radiology.

Interventional procedures are broadly divided into nonvascular (Fig. 1) and vascular (Fig. 2) interventions.

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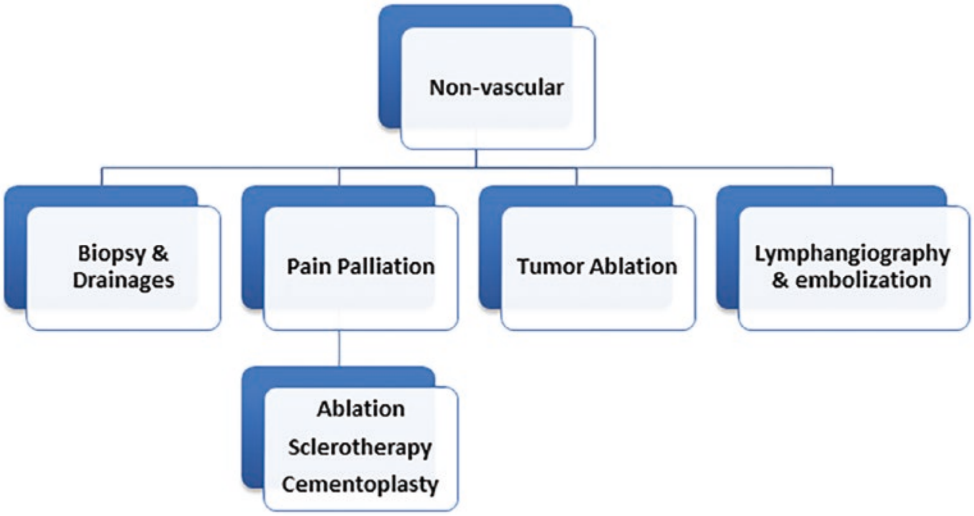

Non-vascular
Biopsy & Drainages
Pain Palliation
Tumor Ablation
Lymphangiography & embolization
Ablation
Sclerotherapy
Cementoplasty

Fig. 1 Non-vascular interventions

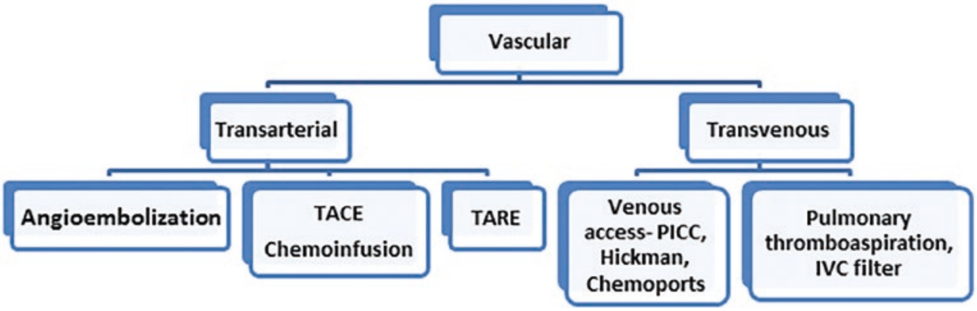

Vascular
Transarterial
Transvenous
Angioembolization
TACE
Chemoinfusion
TARE
Venous access- PICC, Hickman, Chemoports
Pulmonary thromboaspiration, IVC filter

Fig. 2 Vascular interventions

2 Image Guidance for Procedures

Image-guided procedures are performed widely for almost all organ systems to diagnose and characterize focal lesions and organ dysfunction. Ultrasonography (USG) is radiation-free, widely available, and the most commonly used modality for image-guided procedures since the images are in real-time and can be used for solid abdominal organs and lymph nodes of neck region [1]. Computed tomography (CT) is the preferred image guidance modality to target lung and bone lesions and biopsy small abdominopelvic lesions or collections requiring hydro-dissection. CT fluoroscopy reduces the patient's scan time and radiation dose and allows the operator to be present within the CT procedure room. Fluoroscopy is mainly used to perform a guided bone biopsy, and few nonvascular procedures like drainage obstructed biliary or urinary system. Digital subtraction angiography (DSA) is a minimally invasive test used to image the blood vessels when CT or MRI scanning is inconclusive. As the name suggests, bone and soft tissues (stationary) are digitally subtracted when contrast is injected into the vessels, rendering them visible because of the flowing blood. DSA is regularly used for any arterial or venous interventions.

Magnetic resonance imaging (MRI) is not extensively used as an ultrasound or CT scan for targeting a lesion. Breast, prostate, and bone biopsy is done using MRI at a few centers, and the instruments should be MR compatible.

Fusion imaging is used when images from one modality are superimposed on the images from another modality like ultrasound and CT fusion, ultrasound and MRI fusion, PET-CT fusion, PET-MRI fusion, or MRI-DSA fusion. This technique is used when the lesion is seen in one modality, and a different modality is used to target the lesion. For example, real-time USG-guided biopsy or RFA of lesions not seen on ultrasound but visible on CT, MRI, and PET-CT.

3 Patient Evaluation and Peri-procedural Care

Clinical evaluation of the patient includes obtaining a detailed history of the illness and performing a thorough clinical examination. The specific details that need to be asked include a history of allergies, previous reaction to contrast media, any illness such as diabetes leading to nephropathy, history of bleeding tendencies, and ongoing antiplatelet or anticoagulation medications.

3.1 Laboratory Tests

The following are a few relevant blood tests that are requested before IR procedures:

- Complete blood count
- Renal function tests: especially in CT-guided biopsy and interventions or when DSA is being performed, which would require the injection of iodinated contrast
- Prothrombin time, INR
- Fibrinogen when thrombolysis is planned
- 2D Echo before procedure requiring administration of chemotherapeutic drugs which are cardiotoxic like Doxorubicin

Antibiotic prophylaxis is started before a few procedures, per hospital policy and culture sensitivity reports. These include the following:

- Biliary procedures (Bilio-enteric fistula / anastomoses)
- Genitourinary procedures
- Drainage of suspected abscesses
- Embolization intended to invoke target ischemia/infarction (Single shot antibiotic)
- Ablation of tumors
- Biopsies (transrectal route)

If a patient is a known diabetic, sugar level optimization, and antidiabetic drug/dosage modification are done before the procedure. Those with a deranged renal function test would require optimization of serum creatinine. Adequate nephroprotection should be provided if iodinated contrast is being injected in such cases by proper hydration before, during, and after the procedure.

4 Non-vascular Interventions

4.1 Percutaneous Image-Guided Biopsy (Fig. 3)

General indications for a percutaneous image-guided biopsy are mentioned below. Few situations where nonpercutaneous biopsy is performed have been mentioned in the relevant section.

4.1.1 Indications

- Biopsy of a mass lesion for histopathological diagnosis of primary malignancy and immunohistochemistry adding to prognostication.
- Investigation of organ dysfunction, especially post-chemotherapy parenchymal dysfunction.

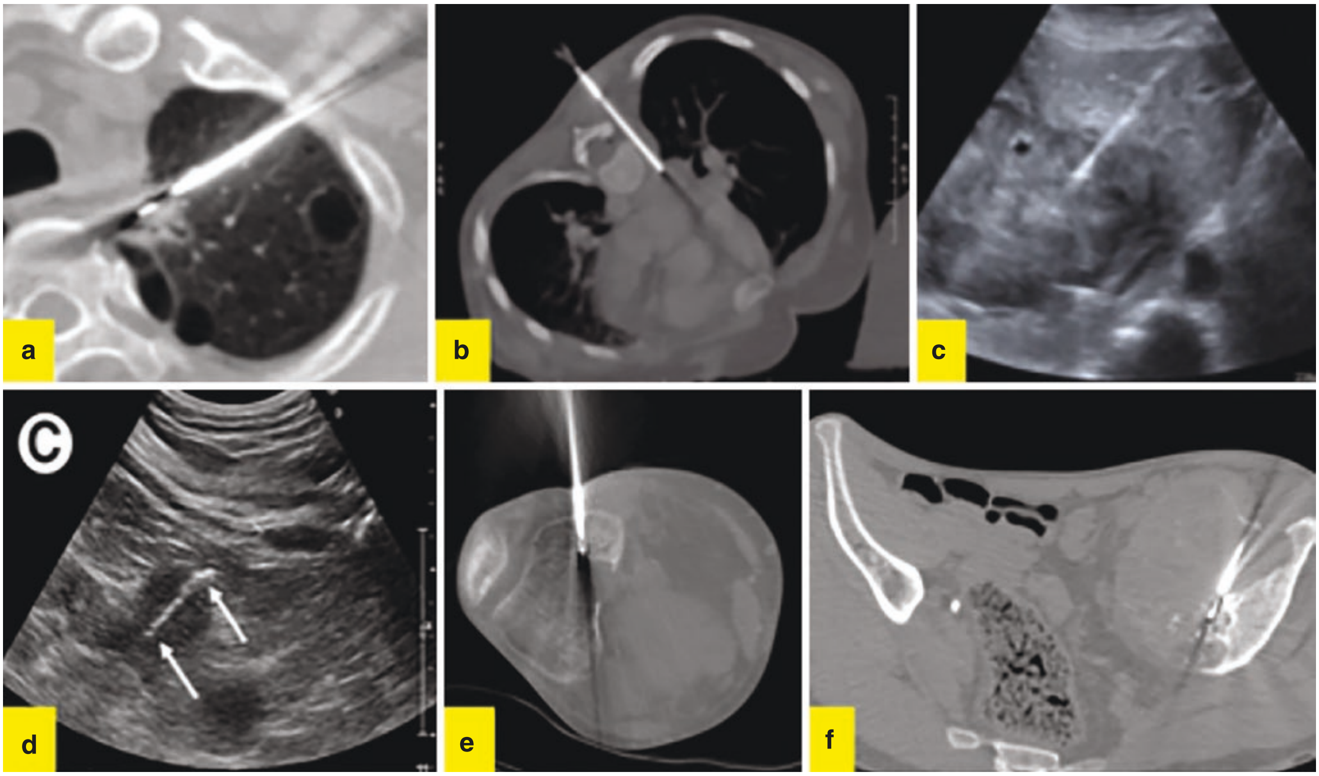


Fig. 3 Biopsies for (**a**) lung nodule, (**b**) subcarinal lymph node with an extrapleural approach using hydrodissection, (**c**) liver lesion, (**d**) renal lesion, (**e**) anteromedial approach for operable primary bone tumor, (**f**) and suspected chondrosarcoma

Table 1 Complications

All locations	Liver	Renal	Lung	Bone
Bleeding	Subcapsular hematoma	Hematuria	Hemoptysis	Osteomyelitis
Infection	Portal vein injury	Urinary leak	Pneumothorax	Fractures
Needle track seeding	Gall bladder injury	Urinoma	Hemothorax	Fat embolism
	Pneumothorax	Subcapsular hematoma leading to PAGE kidney	Air embolism	Neurological injury

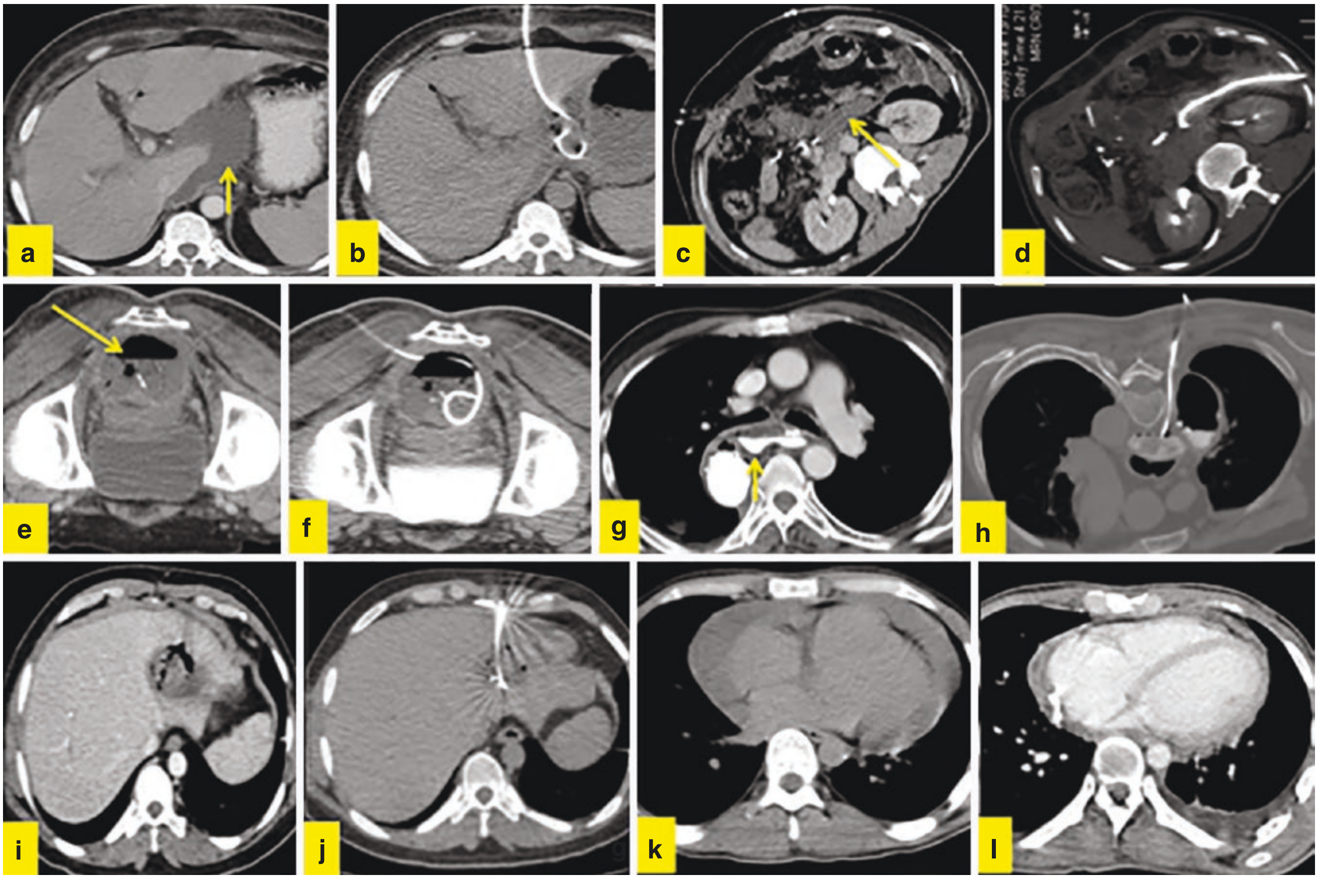


Fig. 4 (**a**, **b**) Lesser sac collection drainage, (**c**, **d**) post Whipple's collection drainage, (**e**, **f**) presacral collection drainage, (**g**, **h**) mediastinal collection drainage, (**i**, **j**) liver abscess pigtail, and (**k**, **l**) pericardial pigtail

- Biopsy of enlarged lymph nodes and metastases, thus allowing for accurate staging and altering management decisions.
- A sampling of infection for culture and sensitivity. Monitoring treatment response

4.1.2 Procedure Contraindications

- Coagulopathy (relative—can be done after correction of clotting factors).

4.1.3 Complications

Table 1 lists complications common to all locations and a few complications specific to particular sites.

4.2 Image-Guided Drainages (Fig. 4)

IR plays a significant role in the drainage of collections, which is a source of infection and septicemia, particularly in postoperative and post-chemotherapy patients.

- Postoperative collections—operative bed collections, anastomotic site leaks. Post operative leak - in iatrogenic biliary injury or ureteric injury
- Obstructive cholangitis
- Obstructive pyelonephritis
- Empyema/pleural effusion
- Pericardial fluid drainage. Indwelling catheter can be placed in cases with recurrent ascites

4.2.1 Pre-procedure

- The patient is started on broad-spectrum antibiotics.
- CT is the preferred modality for postoperative collections as ultrasound has limitations in penetrating gaseous interfaces. However, if a collection is well visualized on sonography, drainage can be done under ultrasound guidance.
- 16- or 18-gauge Trocar needle is routinely used for aspiration. If pus is obtained, a drainage catheter is placed within the collection.
- A sample of aspirated fluid is sent for gram stain along with culture and sensitivity.

4.2.2 Post-procedure

- Adequate care of the catheter is taken to avoid pull-out, and the drain output is measured both quantitatively and qualitatively.
- Antibiotics are changed as per the culture sensitivity report.
- Removal of catheter: The drainage catheter is removed when there is an overall improvement in the clinical well-being of the patient with the resumption of appetite and normalization of white cell count. On imaging, there should be a disappearance of the collection or a significant decrease in the size of the collection and the catheter output less than 10–15 mL daily [3, 4].

4.3 Tumor Ablation

Image-guided tumor ablation is a minimally invasive technique to treat focal tumors by inducing irreversible cell injury through various modes involving chemical injections and thermal or nonthermal energy (Fig. 5). These techniques are now widely used to treat liver, kidney, lung, and bone and soft tissue tumors. In some circumstances, especially for painful bony lesions, it is also finding wider application for pain palliation to improve the quality of life. Its advantages compared to surgical resection include less operative times, minimally invasive, lesser mortality and morbidity, lower cost, and the ability to treat patients who are unsuitable for surgery.

4.3.1 Thermal Ablation Modalities

Thermal ablation strategies increase or decrease the temperature of target tissues to induce irreversible cellular injury. Radiofrequency energy-based systems (RFA) and Microwave (MWA) remain the most widely used modality for the ablation of tumors present in any accessible site, but alternatives include high-intensity focused ultrasound (HIFU), and laser. Cryoablation, which uses hypothermia at freezing temperatures, is also used for focal thermal tumor ablation, especially for renal carcinoma and musculo-skeletal tumors [5].

Radiofrequency

Mechanism of action: When tissues are heated to >60 °C, irreversible cell death occurs due to coagulation necrosis. An electrical circuit is formed where the current loop comprises a generator, cables, electrodes, and body tissue as the resistive element [6] (Fig. 6). The RFA generator can be either monopolar or bipolar, a temperature-based system, or an impedance-based system.

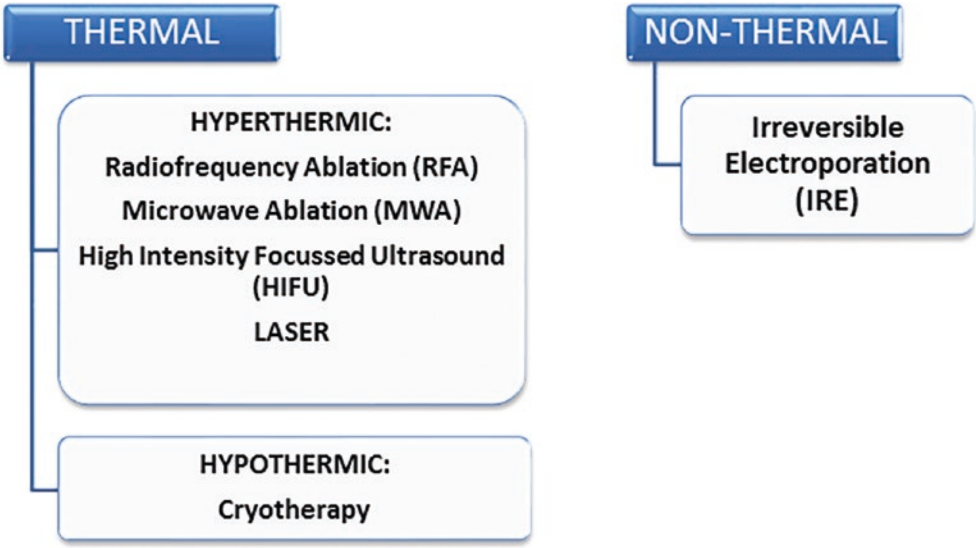
Advantages: Cost effective.

Disadvantages: Heat sink effect, grounding pad burns.

Microwave

Mechanism of action: In microwave ablation (MWA), the inserted applicators function as antennae, and external energy is at 1000–2450 MHz, which causes rotation of the polar molecules. Frictional forces oppose the molecular rotations, and as a result, this converts the rotational energy into

Fig. 5 Modes of Ablation


THERMAL
HYPERTHERMIC:
Radiofrequency Ablation (RFA)
Microwave Ablation (MWA)
High Intensity Focussed Ultrasound (HIFU)
LASER
HYPOTHERMIC:
Cryotherapy
NON-THERMAL
Irreversible Electroporation (IRE)

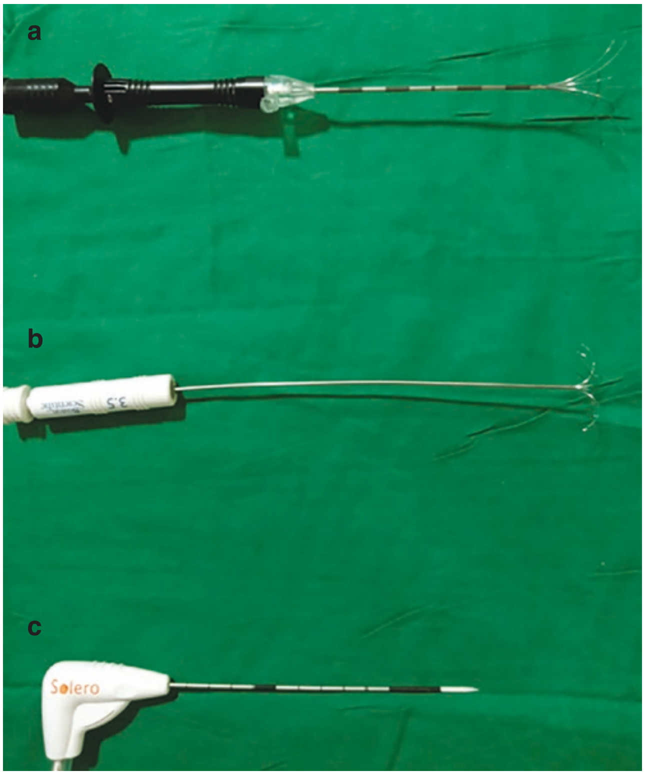


Fig. 6 (**a**, **b**) Radiofrequency ablation electrodes and (**c**) microwave antenna

heat. It can attain higher temperatures than RFA, reaching up to 123 °C.

Advantages: Microwaves readily penetrate through biological materials, including those with low electrical conductivity (e.g., lung, bone) and dehydrated or charred tissue. Microwave ablation reaches higher temperatures more efficiently, does not require grounding pads, and the ablation zone is not affected by surrounding blood vessels, resulting in the heat sink effect [7].

Disadvantages: Technical difficulty with surface lesions Table 2.

Cryoablation

Cryoablation refers to a thermal-based ablation modality that induces tissue injury and cell death using hypothermia at freezing temperatures. It destroys tissue through alternating sessions of freezing at very low temperatures, followed by tissue thawing. Cryoprobe is placed on or inside a tumor using appropriate imaging guidance, and liquid forms of inert gases like helium or nitrogen are circulated through the hollow cryoprobes, which results in cooling of the surrounding tissues to lethal temperatures.

Mechanism of action Cryoablation induces direct cellular injury by freezing and indirect injury through multiple mechanisms, including altering the cellular microenvironment. The temperature range of −20 to −40 °C can result in cell death [8]. Following are the mechanisms of cellular injury due to cryoablation:

Table 2 Comparison between RFA and MWA

	RFA	MWA
Mechanism	Electric current	Electromagnetic energy
Heating	Nonuniform	Uniform
Procedure time	More	Less
Intratumoral temperature	Less	More
Ablation zone	Unpredictable	Predictable
Heat sink effect	Present	Less susceptible
Periprocedure pain	More	Less
Lesion treated at one time	Single	Multiple
Ablation volume	Small	Large
Grounding pad	Present thus can lead to thermal burns	Absent
Abscopal effect	Yes	No

1. Osmotic dehydration causes high intracellular solute concentration leading to dysfunction of the enzymatic systems, damage to cellular proteins, and cell membrane injury.
2. Intracellular ice formation occurs, causing cell organelle and cell membrane injury.
3. Vascular injury consists of damage to the vessel wall [9].

Advantages: Decreased procedure-related pain, risk of thermal injuries to adjacent organs is less compared to hyperthermic ablations, improved real-time visualization of the ablated area in the form of ice ball, and ability to place multiple applicators simultaneously.

Disadvantages: Increased risk of bleeding.

Irreversible Electroporation

Percutaneous irreversible electroporation (IRE) is a relatively new ablation modality becoming increasingly popular due to its application in critical areas, which can be attributed to its nonthermal ablation modality.

Mechanism of action: Several microseconds to milliseconds of long pulses of electric current are passed into the target tissue, which generates an electrical field up to 3 kV/cm. This results in irreversible damage to the cell membrane leading to apoptosis and cell death.

Advantages: IRE appears to limit damage to more collagenous tissues and nerves and has the advantage of its application in thermally sensitive areas (e.g., in the pancreas near major bile ducts and large blood vessels) or neural structures [10]. At present, the maximum use of IRE has been in the treatment of locally advanced pancreatic cancer, and it is also finding wider application in hilar liver tumors.

Disadvantages: Cost, a technically more demanding procedure requiring simultaneous placement of multiple electrodes parallel to each other, risk of cardiac arrhythmias.

5 Vascular Interventions

A few terminologies about vascular interventions are mentioned later. The description of procedures is given in this chapter's relevant section.

Transarterial treatment includes those procedures which are performed through the arterial route. The term selective catheterization means cannulating an artery that is supplying the target area. Super-selective catheterization refers to advancing the catheter (usually a microcatheter less than 3 Fr in size) further distally into the artery as far as possible, which would predominantly supply the area of interest.

5.1 Trans-arterial Embolization (Angioembolization)

It involves angiography with embolization of the neoplastic vascularity for vascular tumors with embolic materials such as gel foam and PVA particles. It is mostly done for preoperative devascularization of tumors (e.g., juvenile nasopharyngeal angiofibromas) or to control bleeding from a ruptured tumor (e.g., hepatocellular carcinoma) or tumor infiltrating into a major artery (e.g., carotid blow out by lymph nodal mass).

5.2 Transarterial Chemoembolization

Transarterial chemoembolization (TACE) refers to local intra-arterial administration of chemotherapeutic agents followed by embolization of the tumor with permanent or temporary embolic material.

5.3 Transarterial Chemoinfusion

It is defined as the injection of chemotherapeutic drugs with or without ethiodized oil in the tumor feeding vessels without embolization.

5.4 Transarterial Radioembolization (TARE)

TARE involves the administration of the Yttrium-90 (Y90) radioisotope into the tumor-feeding arteries in the form of glass or resin spheres. Radioembolization is a misnomer as there is no or minimal embolic effect of the Y90 spheres. Thus, selective internal radiation treatment (SIRT) is a more appropriate term for this treatment.

6 Pulmonary Interventions

6.1 Endobronchial Ultrasound-Transbronchial Needle Aspiration (EBUS-TBNA)

Endobronchial ultrasound-guided transbronchial fine-needle aspiration (EBUS-TBNA) is a novel, minimally invasive method to sample mediastinal or hilar lesions using real-time guidance [11]. It involves targeting lymph nodes or other peribronchial lesions under ultrasound guidance (ultrasound probe mounted over the flexible bronchoscope, Fig. 7a) with a dedicated EBUS-TBNA needle.

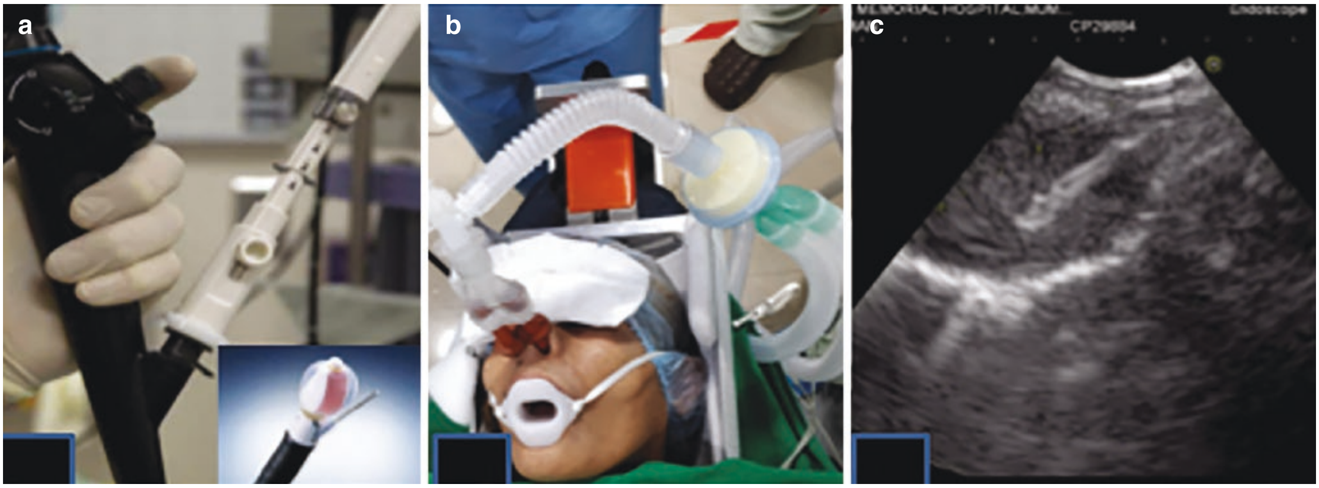


Fig. 7 (**a**) EBUS scope with the needle in the channel, (**b**) nasopharyngeal airway, and (**c**) endobronchial ultrasound image with the sampling needle in a lymph node

6.1.1 Indications

1. Mediastinal staging for nonsmall cell lung cancer (NSCLC).
2. To determine the cause/etiology of unexplained mediastinal lymphadenopathy.
3. As a research tool for tissue banking samples for later studies.

6.1.2 Advantages

- EBUS is a minimally invasive and safe procedure compared to mediastinoscopy.
- It can be performed on an outpatient basis using local anesthesia and conscious sedation.
- Real-time imaging allows the sampling of lymph nodes even smaller than 10 mm in the short axis and near major blood vessels (Fig. 7c).
- EBUS can access various levels of lymph nodes in the mediastinal and hilar lymph nodes with high sensitivity.

6.1.3 Complications

- No major complications.
- Reported minor complications are agitation, cough, hypoxia, laryngeal injury, fever, bacteremia, bleeding, and pneumothorax.

6.1.4 Disadvantages

The tissue cores are inferior to cores obtained from percutaneous biopsy

6.2 Ablation of Lung Tumors

Tumor ablation can be performed in patients with primary lung cancer and pulmonary metastases who are high-risk candidates for surgical resection.

6.2.1 Indications

- Stage I NSCLC
- Pulmonary metastases
- Residual/recurrent disease

6.2.2 Ablation Techniques

- Radiofrequency ablation
- Microwave ablation
- Cryoablation

6.2.3 Technique

- Imaging guidance with CT (Fig. 8a, b).
- RFA, MWA—ablation protocol as per device specifications.
- Surrounding GGO indicates adequate ablation (Fig. 8c, d).

6.2.4 Follow-Up

- PET avid lesions are followed up with locoregional PET, otherwise followed by CECT.
- Follow-up is done at 4-6 weeks, three-monthly for a year, and six-monthly subsequently.
- Response to ablation:
  - Less than a week: Ground-glass opacities (GGO) (the size of the lesion can be increased secondary to GGO)

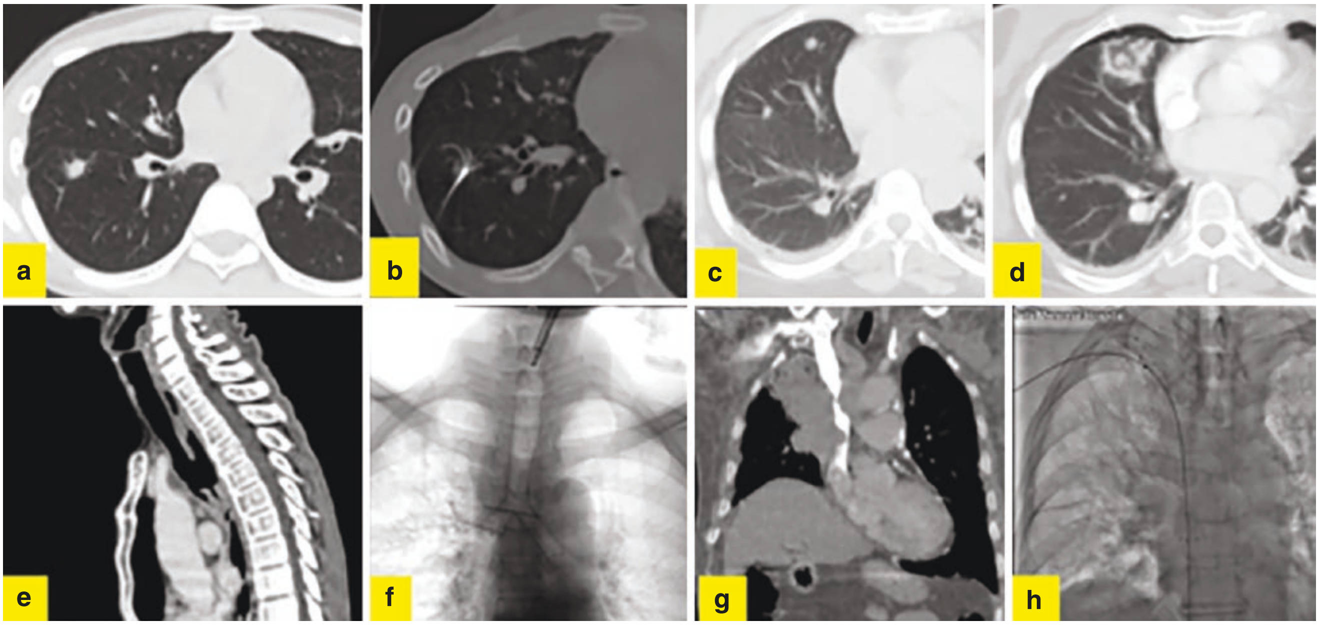


Fig. 8 (**a**, **b**) RFA of lung nodule. (**c**, **d**) Pre- and post-ablation image showing post-ablation surrounding ground-glass opacities. (**e**, **f**) Tracheal stenting for malignant trachea-esophageal fistula. (**g**, **h**) Stenting for SVC syndrome

Table 3 Complications of lung tumor ablation

Complication	Incidence (%)
Pneumothorax	11–52
Pain	0.6
Aseptic pleuritis	2.3
Hemorrhage	0.3–0.9
Bronchopleural fistula	0.3
Cavitation	14
Needle tract implantation	0.1
Infection—lung abscess	1.6

- One week to 2 months: Cavitation
- After 2 months, cavitation undergoes scarring
- At 6 months, minimal changes other than progressive involution of the cavity
- The lesion can show decrease in size or can disappear, can become fibrotic/atelectatic or cavitate

6.2.5 Complications (Table 3)

Outcome

The 3-year cancer-specific survival for stage 1 NSCLC ranges from 59% to 88% [12]. The 3-year cancer-specific survival rates in the cryotherapy, ablation, and surgical resection groups were 90.2%, 90.6%, and 87.5%, respectively [13].

6.3 Tracheal Stenting

6.3.1 Indications

- Central airway obstruction—The airway lumen can be compromised due to an intrinsic tracheal lesion or secondary to external compression.
- Malignant trachea-esophageal fistula [14].

The airway is best evaluated by computed tomography (Fig. 8e) and bronchoscopy to know the etiology, severity, and extent of the stricture and the dimensions of the airway, both proximal and distal, to the stricture.

6.3.2 Image Guidance and Procedure

Tracheal stenting is done under bronchoscopic and fluoroscopic guidance (Fig. 8f). A rigid bronchoscope/tracheoscope is introduced into the airway and placed beyond the vocal cords. Bronchoscope/Tracheoscope not only supports the stent system being introduced but also offers quick access to the airway by allowing ventilation and suctioning during and immediately after the procedure if required. A flexible bronchoscope is passed through this, and the site of stent placement is marked using fluoroscopic and bronchoscopic guidance. The tracheal stent(s) is deployed using the extrinsic skin markers as a reference under fluoroscopic guidance. If the stricture is tight, a guidewire may have to be passed beyond the obstruction, and a stent tracked over it to place it in the desired location.

In situations involving the distal carina and its bifurcation, a “Y”-shaped stent would be required compared to a single stent in case of stricture proximal to the carina.

6.3.3 Complications

- Bleeding
- Tracheobronchial injury
- Arrhythmias
- Stent migration
- Stent infection

6.4 Superior Vena Cava Obstruction

SVC obstruction (also known as SVC syndrome) results in significant narrowing of the SVC, resulting in reduced venous return to the right atrium. It can be caused by extrinsic compression by primary or metastatic tumors or enlarged lymph nodes compressing the superior vena cava (Fig. 8g), central venous access-related benign stenosis or occlusion, and postoperative changes leading to stenosis.

Contraindications to SVC stenting include severe cardiac ailment, coagulation disorders, and chronic venous thrombosis.

The procedure is done under DSA guidance. The narrowed SVC segment is balloon-dilated (venoplasty) to increase the lumen diameter in case of a benign stricture. If the diseased portion recoils or, in case of malignant obstruction, a stent is placed across the stricture to maintain the antegrade flow of blood (Fig. 8h) [15]. Thrombolysis can be considered prior to stenting in cases with bland thrombus in SVC due to chronic venous obstruction.

6.4.1 Complications

The complication rates of stenting for SVC obstruction are very low but include:

- Transient cardiac arrhythmias
- Stent migration
- Thrombus formation and stent stenosis/occlusion
- Migration of thrombus leading to pulmonary embolism
- Infection

7 Hepato-Biliary Interventions

7.1 Transjugular Liver Biopsy (TJLB)

Transjugular liver biopsy (Fig. 9a, b) is usually performed in patients with suspected diffuse parenchymal disease, such as cirrhosis, when a percutaneous biopsy is contraindicated.

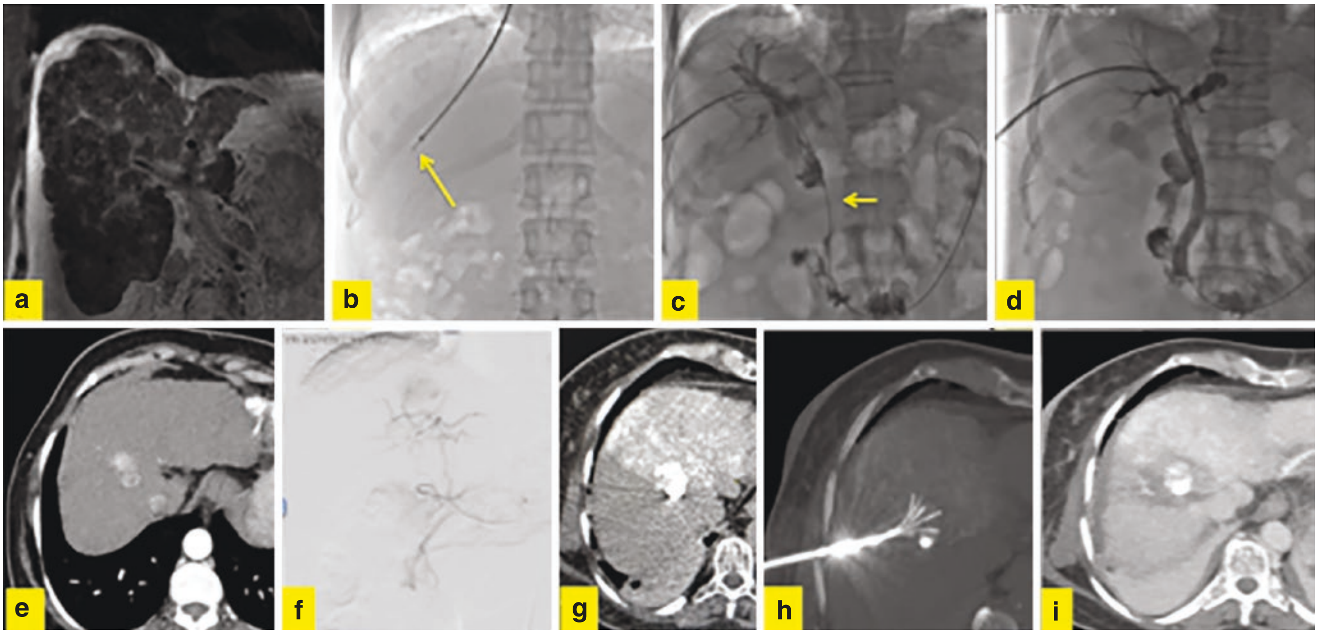


Fig. 9 (**a**) MRI showing diffuse liver disease with gross ascites. (**b**) Transjugular liver biopsy.(**c**, **d**) PTBD and metal stenting. (**e**) Solitary HCC in a k/c/o HCV related CLD. (**f**) cTACE. (**g**) Lipidol-coated liver lesion. (**h**) RFA. (**i**) Post ablation CECT showing the adequacy of ablation

7.1.1 Indications

1. Uncorrectable coagulopathy.
2. Gross ascites.
3. This procedure may also be performed in the absence of coagulopathy or ascites when wedged hepatic vein pressures have to be calculated.

The right internal jugular vein is accessed, and the right hepatic vein is cannulated using fluoroscopic guidance. A hepatic venogram is performed to confirm the identity and patency of the vein. Biopsy from the middle or left hepatic vein can also be performed. The optimal location to perform the biopsy from the hepatic vein is within 3–4 cm of the IVC. Biopsy from more peripheral areas in the hepatic vein risks capsular perforation and intra-abdominal bleeding. After the procedure, vital signs should be monitored for 4 h [16].

7.2 Percutaneous Transhepatic Biliary Drainage and Biliary Stenting

Obstructive jaundice can be caused by many conditions, including benign and malignant diseases. The common causes of malignant biliary obstruction include cholangiocarcinoma, pancreatic and gall bladder malignancies, metastatic lymphadenopathy, infrequently by the liver, and advanced gastric and duodenal malignancies. The essential purpose of biliary interventions in case of obstructive jaundice is to decompress the blocked biliary system and, if possible, to re-establish the physiological flow of bile from the biliary tree to the bowel. Percutaneous transhepatic biliary drainage (PTBD) decreases pain, jaundice, and cholangitis by relieving the obstruction. The drainage of the obstructed biliary system helps improve the liver function before planning for more definitive cancer-directed treatment in the form of surgery or chemotherapy.

7.2.1 Indications

1. Obstructive jaundice due to high biliary obstruction.
2. Failure of endoscopic drainage—percutaneous technique is successful in cases where an endoscopy has failed, as in the case of
    (a) Duodenal stricture
    (b) High or multiple blockages
    (c) Inability to traverse the biliary stricture
    (d) Failure to cannulate papilla
    (e) Post-surgical patients with altered anatomy or biliary enteric anastomosis
3. Biliary leaks.

7.2.2 Contraindications

1. Uncorrectable coagulopathy
2. Gross ascites
3. ECOG >2

Magnetic resonance cholangiopancreatography (MRCP) is essential to evaluate the extent and severity of biliary dilatation and the level of obstruction. PTBD and stenting (Fig. 9) are performed with ultrasound and fluoroscopy guidance. Percutaneous cholangiography is first used to evaluate the exact level and extension of the stenosis and to identify the most appropriate liver segments for drainage. A catheter can be placed for external drainage only or externally as well as internally into the duodenum (internal-external drainage) to bring down the bilirubin to an acceptable level for surgery. Self-expanding metallic stent(s) (SEMS) can be placed into narrow segments for inoperable cases [17, 18]. Patients undergoing metal biliary stenting are usually treated with palliative intent and are started on appropriate chemotherapy once bilirubin levels are reduced to <3 mg/dL.

8 Hepatocellular Carcinoma

Modified Barcelona Clinic Liver Cancer staging is most commonly used to stage and guide treatment for HCC.

8.1 Ablation

8.1.1 Indications

1. Hepatocellular carcinoma: Ablation is the first-line treatment for BCLC stage 0 (small HCC <2 cm), and the survival rates after ablation are similar to those after surgery for HCC <2 cm [19]. Ablation is also used in BCLC stage 1: HCC <3 cm and <3 lesions, bridge therapy to transplant while patients are on the waiting list, or as an alternative to surgery.
2. Colorectal liver metastases: Patients with liver-limited metastases and having five or fewer liver lesions can undergo ablation with curative intent.
3. Neuroendocrine liver metastases: Ablation can be done with curative intent for NET liver metastases. It also provides an option for symptom relief that decreases tumor burden, preserving most of the healthy liver, can be repeated and is associated with less morbidity than resection.

Ablation has the advantage of being a relatively low-risk, minimally invasive procedure for the treatment of focal liver tumors without significant damage to the surrounding liver tissue.

8.1.2 Ablation Modalities

1. Radiofrequency ablation
2. Microwave ablation
3. Cryoablation

For ablation results to be comparable with hepatic resection in terms of local tumor recurrence rates, a 360° 1-cm-thick tumor-free margin around each tumor should be obtained, which may require overlapping ablations [20].

Targeting the lesion for ablation can be performed with ultrasound or computed tomography (CT) and, less commonly, MRI depending on operator preference, local availability of dedicated equipment, and location of the lesion. Adjuvant techniques like hydrodissection, pneumodissection, artificial ascites, or pleural effusion can be used to separate and thus protect adjacent vital organs. It is a safe procedure with low rates of significant complications [21].

Complications include abdominal hemorrhage, hepatic abscess formation, hepatic infarction, biloma, and skin burns [22].

In patients with HCC, the combination of TACE and RFA is associated with significantly higher overall survival and recurrence-free survival compared to RFA alone, without a significant difference in major complications. This benefit is more critical in HCC larger than 3 cm in diameter (Fig. 9f–i) [23].

Follow-up of patients post-ablation is done at 6 weeks with laboratory investigations (CBC, LFTs, RFTs, and tumor markers) and imaging with multiphasic CECT or dynamic MRI liver.

8.2 Transcatheter Arterial Chemoembolization

Transcatheter arterial chemoembolization (TACE), in particular, has been widely performed in the treatment of HCC and is the recommended first-line treatment option for BCLC stage B patients.

TACE is the standard treatment for BCLC-B HCC patients who fulfill the following criteria: Child-Pugh A or B cirrhosis, patent main portal vein, less than 50% involvement of liver parenchyma by the tumor, ECOG <2, and patients willing for a follow-up. TACE can also treat some BCLC A patients who are unsuitable for ablative treatment or surgery.

Relative contraindications include extrahepatic disease, uncorrectable coagulopathy, biliary obstruction, or a comorbid illness like congestive heart failure. Doxorubicin, the most commonly used chemotherapeutic drug for TACE, needs caution prior to injection in patients with underlying cardiomyopathy or significantly reduced ejection fraction.

Absolute contraindications for TACE are Child C cirrhosis, ECOG >2, and main portal vein tumoral thrombosis

TACE can be of two types:

1. Conventional TACE: The chemotherapeutic drug emulsion is prepared using doxorubicin and iodized oil (lipiodol), infused into the tumoral feeding arteries. Cisplatin or mitomycin may also be given tailored according to the case. The infusion is followed by embolization of the

tumoral neovascularity. When the lesion shows complete coverage with lipiodol or if there is reflux of emulsion into nontarget branches, further injection of the emulsion is stopped (Fig. 9e, f).

2. DEB-TACE: DEB (drug-eluting beads) act as drug carriers and provide better drug delivery into the tumor with lesser systemic toxicity. Drug-eluting beads are loaded with doxorubicin for hepatocellular carcinoma and with irinotecan for DEBIRI-TACE of colorectal liver metastases.

8.2.1 Complications

1. Post embolization syndrome (nausea, fatigue, and low-grade fever)
2. Gastritis, cholecystitis
3. Hepatic decompensation (new-onset ascites, icterus)
4. Rare complications include ischemic bile duct injury, duodenal ulceration, and liver abscess formation

It has been found that the drug toxicity and systemic side effects are lesser in DEB-TACE compared to cTACE because of the sustained and controlled release of the drug.

8.3 Follow-Up

1. Follow-up after TACE includes a detailed clinical examination; serum AFP estimation CECT/MRI at 4–6 weeks to assess response. CECT or MRI can be done at follow-up after DEB-TACE; however, MRI is preferred after cTACE as lipiodol deposition makes it challenging to evaluate for residual enhancement.
2. If bilobar treatment was planned initially, the other lobe is treated in 3–4 weeks after repeating the LFTs.
3. If the follow-up imaging shows residual or recurrent disease or if there is raised serum AFP level, a repeat TACE is undertaken after a gap of 3–6 weeks following the previous session of TACE, only if the Child's status is A or B [24–26].

8.4 Selective Internal Radiation Therapy (SIRT) or Transarterial Radioembolization (TARE)

TARE involves delivering Y90 (yttrium 90) impregnated microspheres selectively through the hepatic artery to the tumor. The Y90 radioisotope is unstable and undergoes decay into the stable element zirconium-90 emitting beta particles, which induce direct destruction of cells of the target tumor. Currently, two Y90 products are commercially available: TheraSphere (glass microspheres) and SIR-Spheres (resin microspheres).

Patient selection for TARE requires history and physical examination. Patients with a poor general condition (ECOG score >2) or expected survival of less than 3 months and deranged liver functions are not candidates for TARE. Preprocedure imaging includes chest computed tomography (CT), either a multiphasic CT abdomen or dynamic magnetic resonance (MR) scan of the liver, and sometimes a bone scan.

Ideal candidates have HCC confined to the liver with a tumor comprising less than 70% of the liver volume. For patients with multiple tumors or HCC in both lobes, the liver function should be preserved for performing sequential treatments for both lobes. Patients with main portal vein thrombosis in whom TACE is contraindicated can be treated with TARE.

TARE requires a pretreatment angiography for accurate mapping of the hepatic vessels, extrahepatic tumoral supply, and the presence of shunting to healthy liver or lungs. Macroaggregated albumin (MAA) lung shunting study is performed before TARE to predict the lung shunt fraction (LSF) and minimize the chances of radiation-induced lung damage. In the ^{99m}Tc-MAA nuclear scan, 4–5 mCi of ^{99m}Tc-MAA is injected into the hepatic artery feeding the tumor, and a SPECT scan is performed. This test is performed to determine whether arteriovenous connections within and surrounding the tumor divert blood flow to the lungs. The administration of Y90 microspheres could thus enter the lungs and cause radiation pneumonitis when TARE is performed in cases with a high lung shunt fraction (>20%).

TARE has been evaluated to be useful in hepatocellular carcinoma (Fig. 10a–d), intrahepatic cholangiocarcinoma, neuroendocrine liver metastases, and colorectal liver metastases (Fig. 10e–h).

The advantages of TARE include cases where TACE cannot be done (e.g., those with portal vein thrombosis), elderly population, cases where TACE has failed, and patients with bilobar disease where more than five lesions are present. In patients with HCC, TARE showed to have a longer time to tumor progression than TACE, thus better serving as a bridge to liver transplant at centers with a long wait time [27, 28].

8.4.1 Follow-Up

The patients are usually followed up after 6 weeks when the clinical condition is assessed primarily for potential adverse effects. Laboratory investigations mainly involve monitoring the liver function tests and tumor markers for disease control (S.AFP, CEA). In the case of sequential bilobar treatment, the next session of TARE to the untreated lobe is performed 4–6 weeks after the first treatment. Imaging with either CT or MRI is usually performed at 6-month follow-up for radiological response assessment.

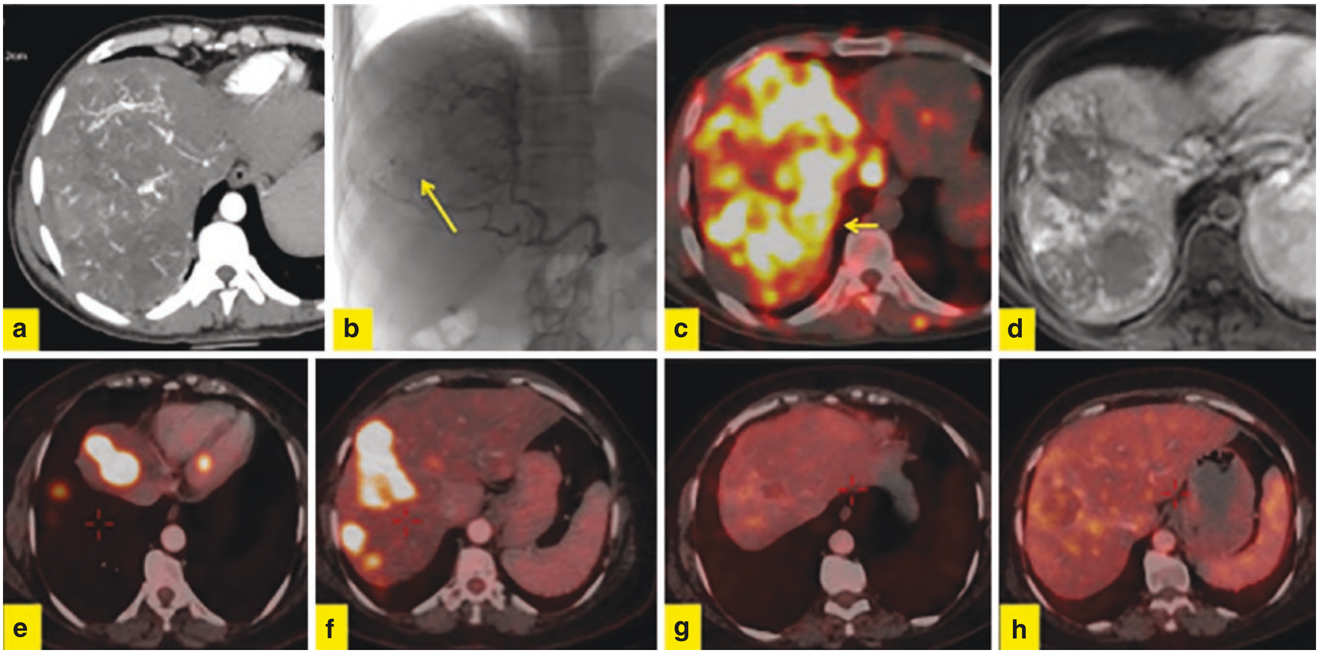
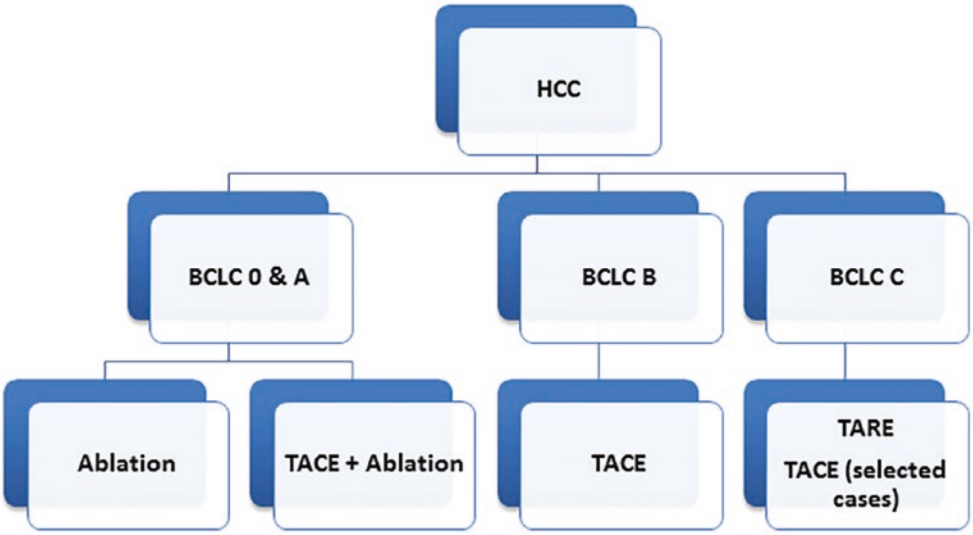


Fig. 10 (**a**) Large HCC invading the portal vein. (**b**) Hepatic angiogram and TARE. (**c**) Post TARE PET to look for drug distribution. (**d**) Follow-up CEMRI shows necrosis within the lesion. (**e**, **f**) Colorectal liver metastases refractory to systemic chemotherapy. (**g**, **h**) Post-radioembolization complete metabolic response on follow-up PET-CT

Fig. 11 Role of IR in the management of hepatocellular carcinoma



8.4.2 Complications

1. Mild clinical side effects after radioembolization include abdominal pain, nausea, vomiting, fatigue, and fever, which usually occur within 4–6 weeks.
2. More severe complications (1–3 months after radioembolization) include gastric ulceration, pancreatitis, radiation pneumonitis) due to nontarget deposition of radioactive beads and liver decompensation.
3. Excessive irradiation of healthy liver parenchyma leads to radioembolization-induced liver disease (RILD), which is thought to be a veno-occlusive disease/sinusoidal obstruction syndrome [29].

The role of IR in managing hepatocellular carcinoma is presented in Fig. 11.

9 Genitourinary Interventions

9.1 Transjugular Renal Biopsy

Transjugular renal biopsy is usually performed in patients with the suspected renal parenchymal disease when a percutaneous biopsy is contraindicated.

9.1.1 Indications

1. Coagulopathy
2. Gross ascites

The renal vein is accessed via the transjugular route, similar to the TJLB procedure described in the previous section. A renal venogram is performed to confirm the identity and patency of the vein, and the biopsy is done with the biopsy gun provided in the TJRB set.

Complications can include persistent hematuria and perinephric hematoma.

9.2 Percutaneous Nephrostomy and Antegrade Ureteric Stenting

It is a procedure in which an external drain is placed in the renal pelvis to relieve the renal pelvis of any obstructive symptoms (Fig. 12a). It could be later converted into internal ureteral drainage by placing plastic (Fig. 12b) or metallic stent. Metallic stents, which can be retrievable or nonretrievable, may be more useful in cases of inoperable malignant strictures for long-term palliation of obstructive uropathy.

9.2.1 Indications

1. Obstructive uropathy
   (a) Extrinsic compression: lymph nodal masses, adnexal masses
   (b) Intrinsic: tumor
   (c) Postoperative stricture
2. Urinary diversion
   (a) Treat urine leak or fistula for postoperative patients
   (b) Decompress urinoma
   (c) Pyelonephritis
3. Access to percutaneous intervention
   (a) Antegrade ureteral stenting
   (b) Stricture dilation

9.2.2 Procedure

Depending on the patient's comfort, the procedure is performed with the patient in a prone, prone oblique, or lateral position. Regular monitoring of the vital signs is recommended during the procedure. The skin is cleaned with an antiseptic solution and draped to maintain the sterility of the procedure.

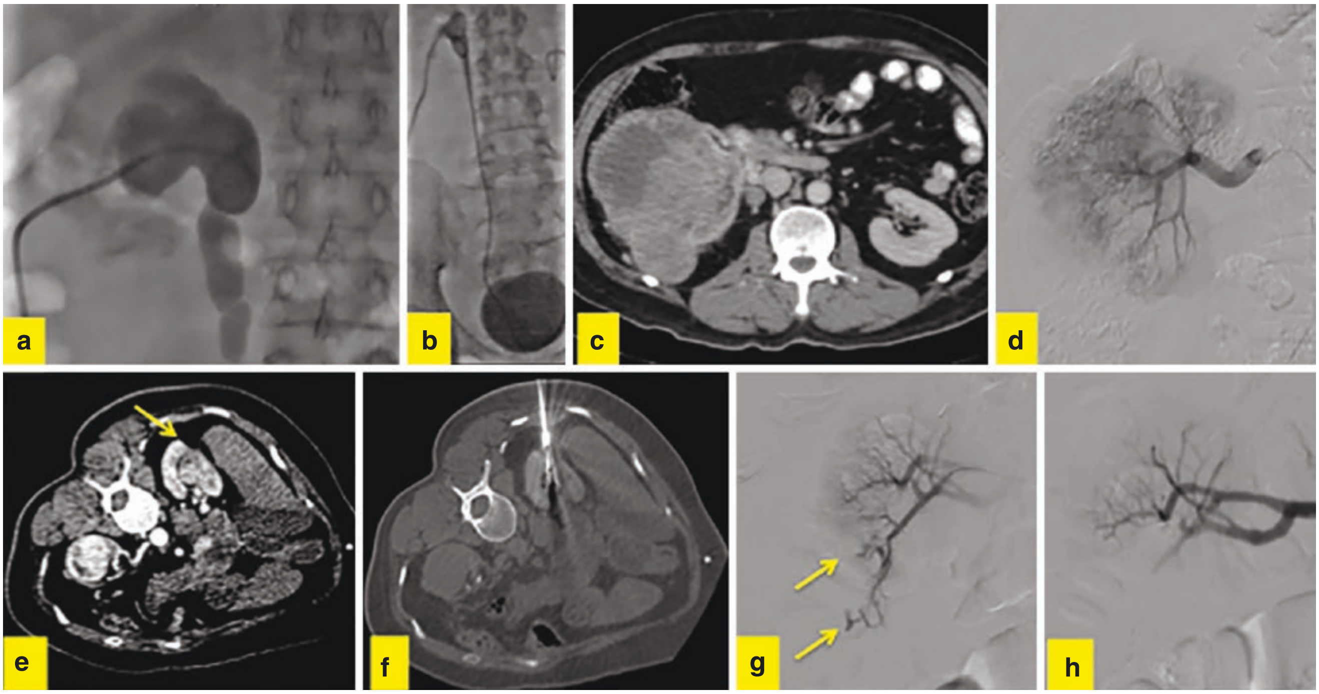


Fig. 12 (**a**, **b**) PCN with antegrade DJ stenting. (**c**, **d**) Metastatic RCC with severe hematuria for angioembolization. (**e**, **f**) RFA for RCC in a k/c/o VHL. (**g**, **h**) Post partial nephrectomy hematuria—coil embolization for pseudoaneurysms

9.2.3 Medications

Preprocedure antibiotic prophylaxis and pain medication is given.

9.2.4 Technique

The procedure is performed under sonography and fluoroscopy guidance.

Sonography is useful when the collecting system is dilated, lower/mid pole calyx is targeted, and an external drain is placed. Fluoroscopic guidance is preferred to puncture the calyx during PCN for an undilated pelvicalyceal system, as in case of a urine leak due to postoperative ureteric injury.

Antegrade ureteric stenting can be done via the access taken for percutaneous nephrostomy after crossing the obstruction with a catheter-guidewire combination [30]. If a ureteric stent is placed for <6 weeks, a polyurethane stent (JJ or DJ) stent is considered, while a silicone ureteric stent can be retained until 6 months without exchange. However, if there is repeated blockage of ureteric stents due to tumor compression or infiltration, a metal stent may be placed in the ureter. Plastic stent exchange needs to be done every 3-4 months to prevent encrustation.

9.2.5 Complications

- Bleeding
- Bowel injury and peritonitis
- Urine leak

9.3 Renal RFA

Renal carcinoma accounts for approximately 4% of all malignancies, and surgical resection remains the standard of care for renal tumors. However, the thermal ablation of a renal tumor can be an alternative treatment modality due to its minimally invasive nature.

9.3.1 Indications

International consensus panels support the following indications for ablative therapy of a small renal tumor that is less than 4 cm (T1a disease)

- Comorbidities that preclude surgery
- Comorbidities that preclude general anesthesia
- Require conservation of renal parenchyma as in case of solitary kidney or renal insufficiency
- Predisposed to multiple tumors in the same kidney (Von Hippel–Lindau syndrome)

9.3.2 Ablation Techniques

Thermal

1. Radiofrequency ablation (Fig. 12e, f)
2. Cryoablation
3. Microwave ablation

RFA and cryoablation are most commonly preferred for the ablation of renal tumors. Cryoablation is preferred in the case of centrally located tumors since it is possible to monitor the iceball formation and prevent damage to the pelvicalyceal system compared to RFA. For peripherally located lesions, both cryo and RFA may be preferred.

Procedure

USG or CT is used to guide the placement of an electrode or applicator. Contrast-enhanced ultrasound (CEUS) or contrast-enhanced CT can be used to aid tumor visualization. Applicators are placed in such a way that the ablation zone covers the entire volume of the tumor, including a margin of normal parenchyma. Overlapping ablation may be required to achieve complete ablation. Pyeloperfusion (cold saline for RFA and warm saline for cryoablation) is performed if a tumor is less than 1 cm from the ureter to prevent thermal injury to the pelvicalyceal system. Hydro dissection with 5% dextrose is done to displace and avoid bowel injury.

Adjuvant Techniques in Renal Tumor Ablation

- In cases with lesion >3 cm, angioembolization is done before ablation to reduce the size of the lesion and also to reduce the risk of bleeding as RCCs are hypervascular tumors.
- In cases with small lesions, preliminary angiography and lipiodol infusion can be done to enhance lesion visibility and thus improve targeting while ablation [31].

Complications

- In 80% of cases, fever or flu-like symptoms (post-ablation syndrome) develop.
- The majority of ablative complications are related to perinephric hematomas and transient hematuria.
- Ureteral strictures and large hematomas are rare. Urinary leak.

Outcomes

In the appropriately selected patients with stage T1a renal cell carcinoma, ablation is an effective treatment option that provides a 5-year efficacy of 97.0% and 5-year recurrence-free survival of 100%. The 5-year overall survival is 97.8%, with a complication rate of 6% [32, 33].

Follow-up interval and modality: Contrast-enhanced cross-sectional imaging follow-up with either CT or MRI at 1, 3, 6, and 12 months after RFA [34].

9.4 Renal Angioembolization

9.4.1 Indications

- Hematuria: postoperative (partial nephrectomy—Fig. 12g, h), post-biopsy.
- As an adjunctive procedure before ablation to reduce size and vascularity.
- Pre-operative devascularization to reduce intraoperative blood loss.
- Palliative to alleviate symptoms of pain and hematuria (Fig. 12c, d) [35].

10 Other Interventions

10.1 Central Venous Access

Image-guided percutaneous central venous access is defined as placing a catheter with its tip in the cavoatrial region or right atrium with the assistance of real-time imaging.

The sonography and fluoroscopy-guided central venous catheter insertion are faster, safer, and better than relying solely on anatomic landmarks.

Central venous catheters can be one of the four types [36]:

1. Peripherally inserted central catheters (PICC)
2. Temporary/nontunneled catheters
3. Permanent/tunneled catheters
4. Implantable ports

Peripherally inserted central catheters (Fig. 13a) are like long intravenous cannula. They extend from the puncture site up to the cavo-atrial junction. The PICC may have one to two lumens and range from 4- to 7-Fr. They are inserted from an upper arm vein, and indications include the following:

- Infusion of chemotherapy
- Infusion of intravenous fluids
- Infusion of blood products
- Infusion of total parenteral nutrition
- Blood sampling

Temporary/non-tunneled catheters (Fig. 13b) are commonly inserted through the internal jugular, made of polyurethane, and range from 6 to 13 Fr in size. They are suited for the delivery of medications, central venous pressure monitoring, and short-term dialysis. Indications include

- Infusion of intravenous fluids
- Infusion of blood products
- Infusion of total parenteral nutrition
- Blood sampling
- Mahurkar catheter—stem cell harvesting

A permanent/tunneled catheter (Fig. 13c) is a central venous catheter that traverses through a subcutaneous tract before entering the access vein. Tunneled catheters are preferred when central venous access is required for more than 2 weeks [36]. The catheter is tunneled subcutaneously for 10–15 cm before entry into the access, preferably the internal jugular vein.

A polyester cuff on the shaft of the catheter provides the catheter security to the subcutaneous tissues, which become incorporated within the tissues.

The advantages of these catheters are decreased risk of infection, reduced risk of inadvertent removal, improved cosmetic appearance, and patient comfort. Indications are

- Infusion of chemotherapy
- Infusion of intravenous fluids
- Infusion of blood products
- Infusion of total parenteral nutrition
- Blood sampling

A subcutaneous infusion port (Fig. 13d) consists of a tunneled central venous catheter that terminates in a subcutaneous pocket where a self-sealing reservoir is implanted [36]. They consist of a single or dual-lumen reservoir hub attached to the catheter. This reservoir hub is implanted in the arm or chest, and the catheter is tunneled to the vein accessed. The port can be accessed by Huber needle. These catheters are used for long-term access, such as for chemotherapy regimes. They have a lower rate of malfunction and symptomatic complications [37] and better cosmetic results. Of all the central venous catheters, ports have the lowest incidence of infection because they are entirely buried beneath the skin.

10.1.1 Complications

- Hematoma
- Cardiac arrhythmias
- Pneumothorax
- Air embolism
- Catheter-related infections
- Venous thrombosis
- Catheter tip migration
- Catheter fracture
- Catheter occlusion/fibrin sheath formation

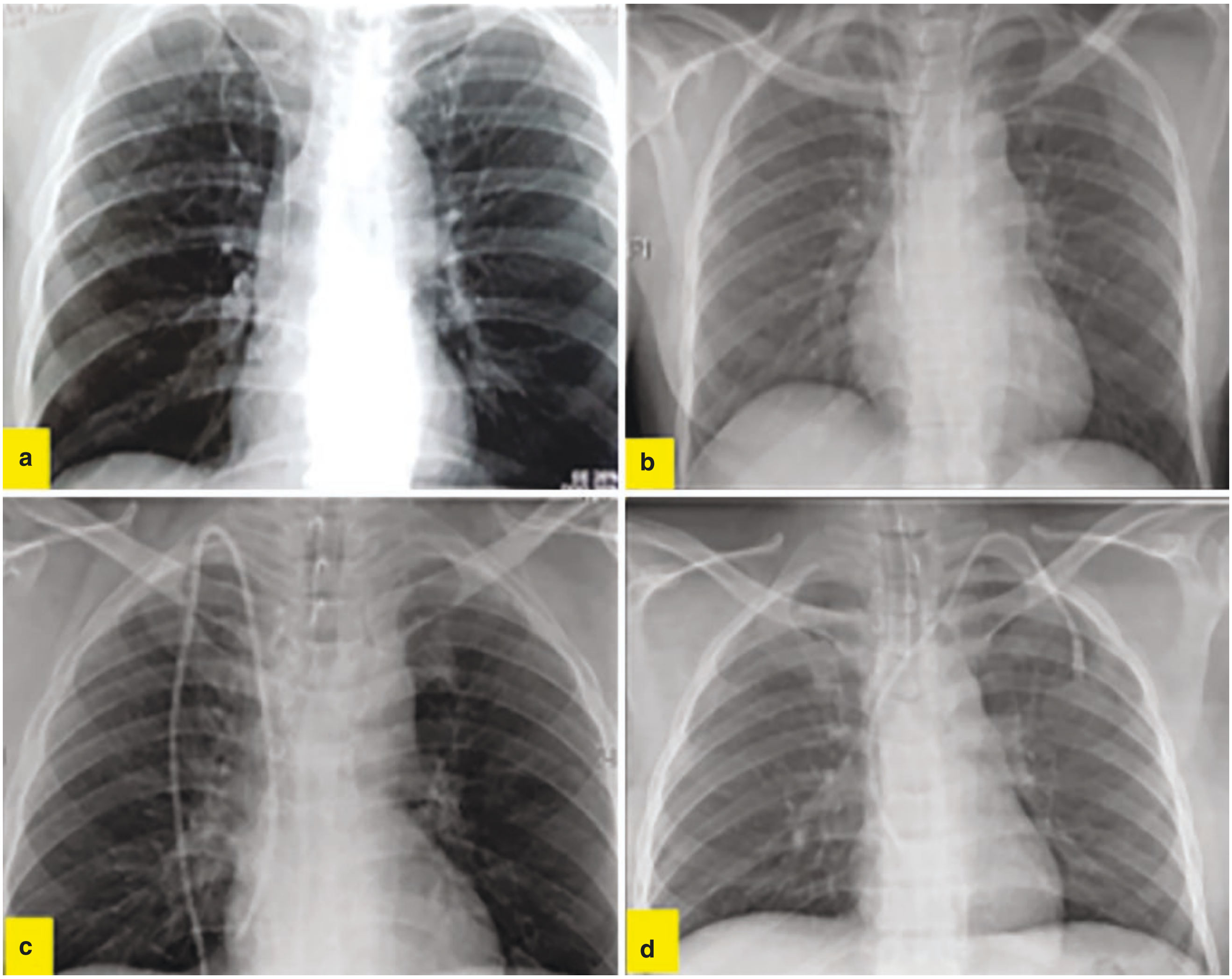


Fig. 13 (**a**) PICC. (**b**) Central line. (**c**) Hickmann. (**d**) Port insertion

10.2 Bone and Soft Tissue Interventions

Ablation, as a minimally invasive treatment modality, has emerged as an alternative to surgery in the management of select tumors of the bone and soft tissues.

10.2.1 Indications

1. Curative treatment for primary bone tumors—osteoid osteoma, chondroblastoma, and osteoblastoma. With the clinical success of ablation being 87–100%, ablation is now considered the gold standard in the treatment of osteoid osteoma (Fig. 14a–d).
2. Palliative treatment of painful bone metastases. Ablation is frequently combined with cementoplasty for pain palliation for weight-bearing bones. Angioembolization can be done before ablation and cementoplasty for vascular metastases like renal carcinoma and thyroid carcinoma (Fig. 14e–i).
3. Palliation of symptoms such as pain in case of nerve involvement or restricted range of movement in cases of fibromatosis (Fig. 14j–m).
4. It can sometimes be used for curative treatment of malignant bone tumors that have a postoperative recurrence and are not candidates for resection [2, 38].

10.2.2 Ablation Modalities

- RFA is the treatment of choice for osteoid osteoma.
- Minimal data is available on MWA and cryotherapy of bone tumors.
- It is mainly done under CT guidance with the resolution of clinical symptoms as an indicator for complete ablation.
- HIFU is used for painful bony metastasis.
- MRI is used in some centers for ablating tumors of the spine. However, this setup would be expensive and requires MRI-compatible instruments [39].

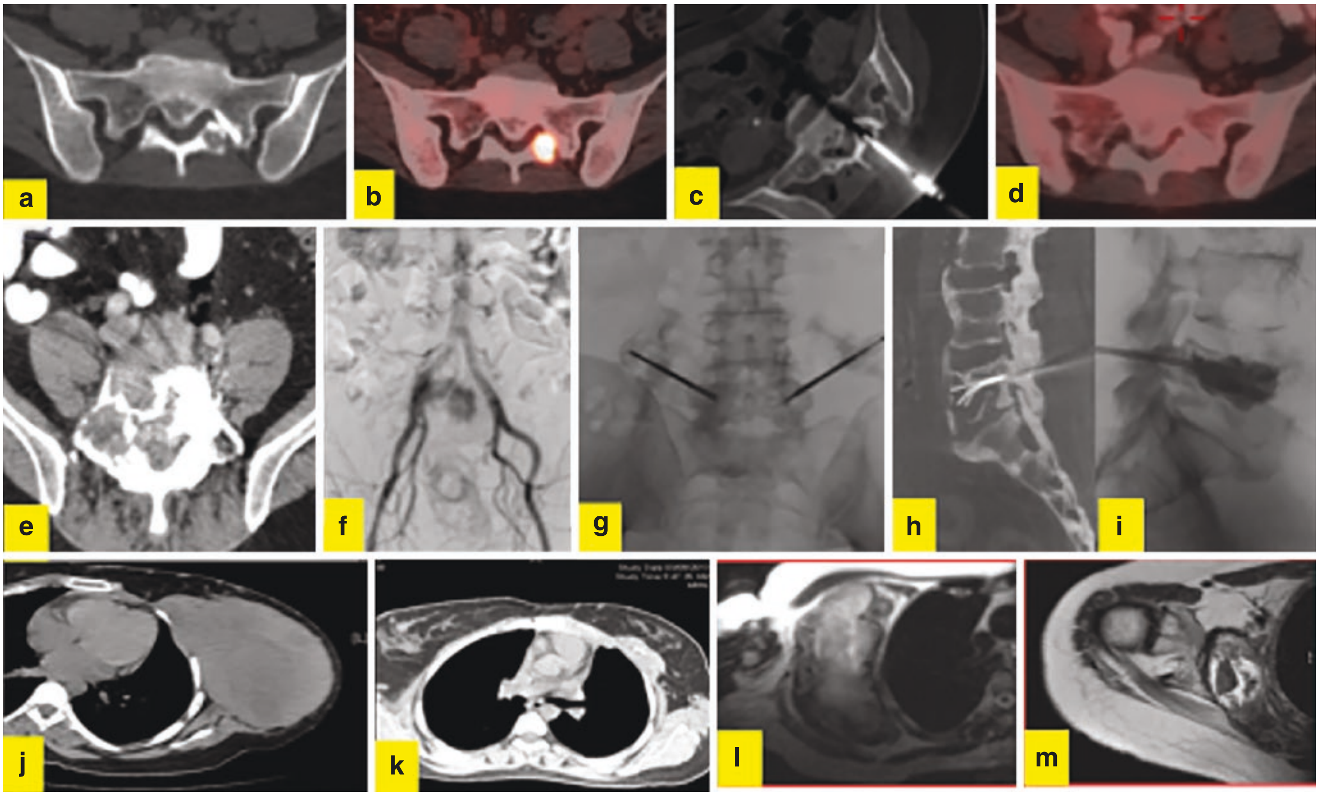


Fig. 14 (**a**–**d**) RFA of sacral (S2) osteoid osteoma. (**e**–**i**) Painful vertebral metastases, angioembolization followed by ablation and vertebroplasty. (**j**–**m**) Ablation for fibromatosis with post-procedure follow-up

10.3 Percutaneous Vertebroplasty

Percutaneous vertebroplasty is a therapeutic, image-guided, minimally invasive percutaneous procedure that involves an injection of radiopaque cement into a painful vertebral body to relieve pain and provide stability. Percutaneous kyphoplasty is a technique whereby expandable balloons are used to restore the collapsed vertebra's height before the cement injection.

10.3.1 Indications

- Painful osteoporotic vertebral compression fractures.
- Painful vertebrae due to malignant infiltration by multiple myeloma, lymphoma, and metastasis.
- Painful vertebrae due to aggressive primary bone tumors such as hemangiomas [40, 41].

10.3.2 Absolute Contraindications

- Asymptomatic vertebral body tumors without fracture
- Cord compression
- Osteomyelitis, discitis, or active systemic infection
- Uncorrectable coagulopathy

10.3.3 Relative Contraindications

- Fracture of the posterior vertebral body wall—increased risk of cement leak and bone fragment displacement.

10.3.4 Procedure

- The procedure is performed under local anesthesia as an outpatient procedure.
- The patient is positioned prone for the lumbar and thoracic levels and supine for the cervical level.
- The classic transpedicular route is employed for the lumbar and thoracic levels. In the cervical vertebrae, an anterolateral approach is used.
- After the placement of bone biopsy needle(s) in the anterior one-third of the vertebral body, radio-opaque vertebroplasty cement is injected under continuous fluoroscopic monitoring.

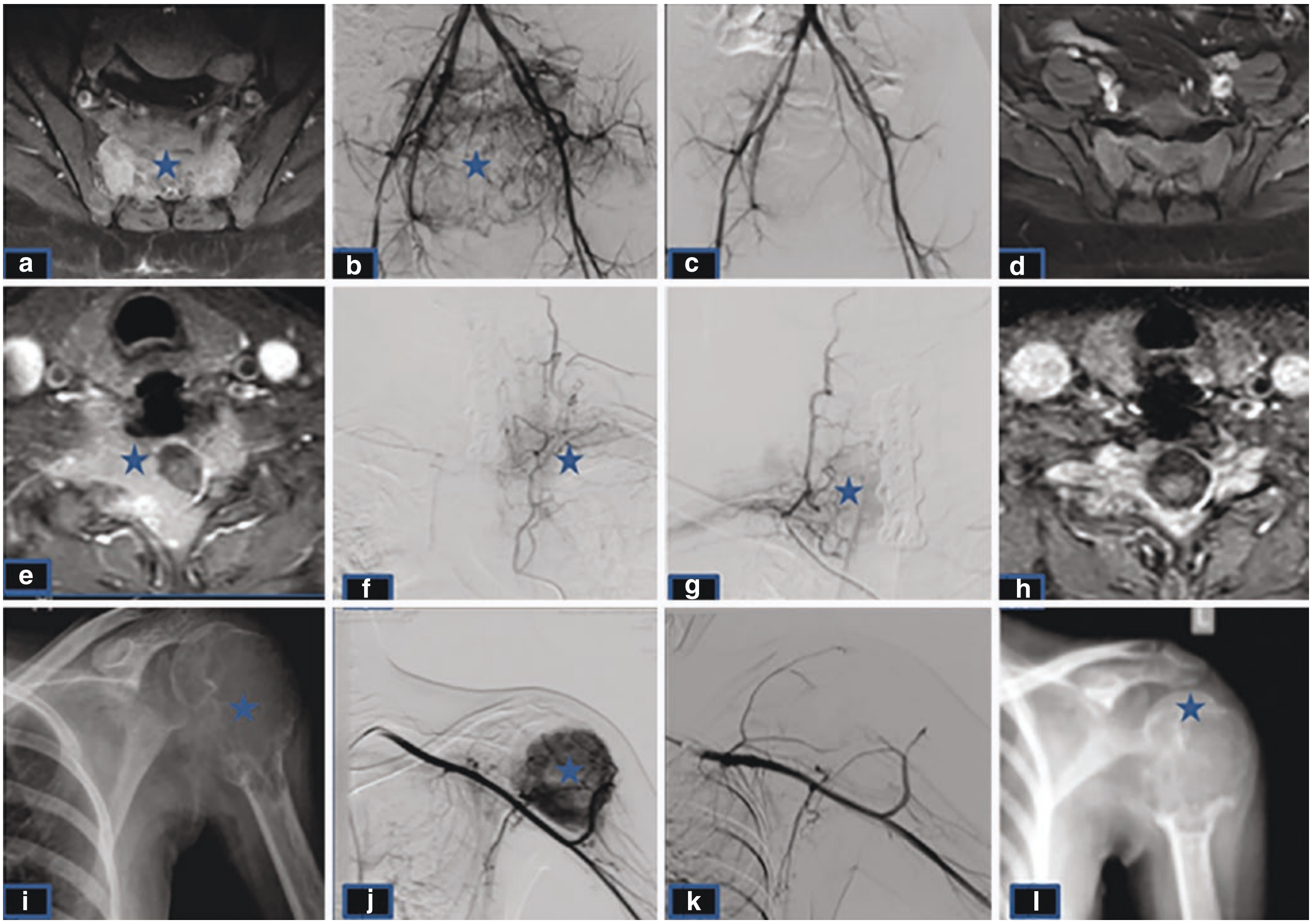


Fig. 15 Angioembolization as definitive treatment for sacral GCT (**a**–**d**), cervical GCT (**e**–**h**), and humeral GCT (**i**–**l**)

10.3.5 Complications

- Cement leakage (epidural space, perivertebral venous plexus, disc space, and paravertebral tissue) is the most frequent complication and is usually asymptomatic.
- Infection occurs in less than 1%.
- Bleeding.

10.4 Angioembolization of Bone Tumors

10.4.1 Indications

- Serial angioembolization with or without denosumab to achieve local control in Sacral giant cell tumors (GCT) or in cases of proximal femoral or humeral GCT where torniquet cannot be tied (Fig. 15).
- Preoperative embolization to reduce intra-operative blood loss and also surgical time—primary osseous tumors included GCT, aneurysmal bone cyst (ABC), osteoblastoma, chondroblastoma, and chondrosarcoma.
- Pain palliation for bone metastases [42–44].

10.5 Ophthalmic Artery Chemoinfusion for Retinoblastoma

Retinoblastoma is the most common eye tumor in children, leading to death within 1–2 years if left untreated. The tools for the management of retinoblastoma include surgery (enucleation), radiation therapy, systemic chemotherapy, and focal therapies (including cryotherapy, laser photocoagulation, and transpupillary thermotherapy). Intra-arterial chemotherapy (ophthalmic artery chemoinfusion) has emerged as one of the effective options for local disease control and has been found very effective as a globe-conserving strategy [45].

The intra-arterial chemotherapy is done under general anesthesia. The technique involves navigating through the internal carotid artery to selectively enter the ophthalmic artery (OA), followed by injection of the chemotherapy drugs specifically into the artery leading to the tumor (Fig. 16d).

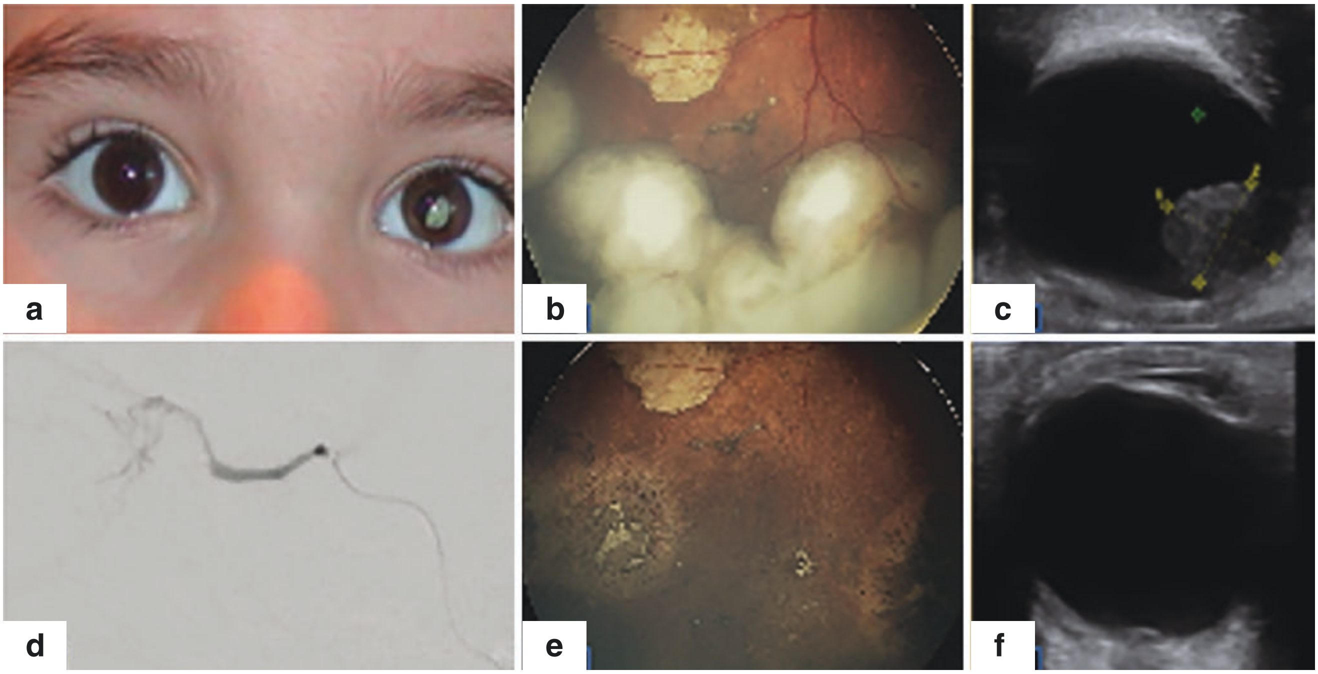


Fig. 16 (**a**) White reflex in a c/o retinoblastoma. (**b**) Ophthalmological examination. (**c**) B scan showing a lesion in the posterior chamber. (**d**) Ophthalmic artery chemoinfusion. (**e**) Follow-up ophthalmological examination. (**f**) Follow-up B scan

The number of sessions for such treatment is 1–5, with most children requiring an average of 2–3 sessions. The child undergoes an eye examination by an ophthalmologist (Fig. 16b, e) and a B scan (Fig. 16c, f) after each session to assess the tumor response to treatment.

The advantages of ophthalmic artery chemoinfusion are as follows:

- Maximum delivery of the chemotherapeutic drug to the tumor and minimum toxicity to other organs of the body.
- Globe can be salvaged in group D disease in 75–84% of cases [46].
- Downstaging to definitive targeted focal therapy like laser therapy.
- OAC can be combined with systemic chemotherapy to salvage the eye in group E disease [47].

10.6 Lymphangiography and Thoracic Duct Embolization

10.6.1 Indications

- Injury to the thoracic duct occurs commonly during thoracic or neck surgeries (up to 3% of esophagectomies), resulting in chylous pleural or pericardial effusion.
- Chylous ascites may develop after surgery involving extensive thoracoabdominal, retroperitoneal, or pelvic nodal dissection.

In patients with leaks persistent with conservative management, intervention is performed. The options include surgical ligation and percutaneous thoracic duct embolization. Percutaneous embolization of the thoracic duct has an approximately 80% success rate in controlling chylous leaks due to thoracic duct injury.

10.6.2 Procedure

- Lymphangiography can be done by injecting lipiodol into the inguinal lymph nodes under ultrasound guidance (instead of the traditional technique of cannulating the lymphatic channel in the dorsum of the foot after injecting methylene blue in the first web space for identification). The flow of lipiodol is visualized with intermittent fluoroscopy (Fig. 17a).
- The thoracic duct can be accessed after its opacification by percutaneous transabdominal puncture under fluoroscopic guidance.
- Alternatively, it can also be catheterized via the transvenous route where it enters the left subclavian vein (Fig. 17b, c).
- When access to the thoracic duct is gained, a microcatheter is advanced, and embolization is performed with multiple coils and *N*-butyl cyanoacrylate (n-BCA) glue (Fig. 17d).
- If the access to cisterna chyli fails, thoracic duct disruption can be achieved by puncturing the cisterna chyli multiple times.

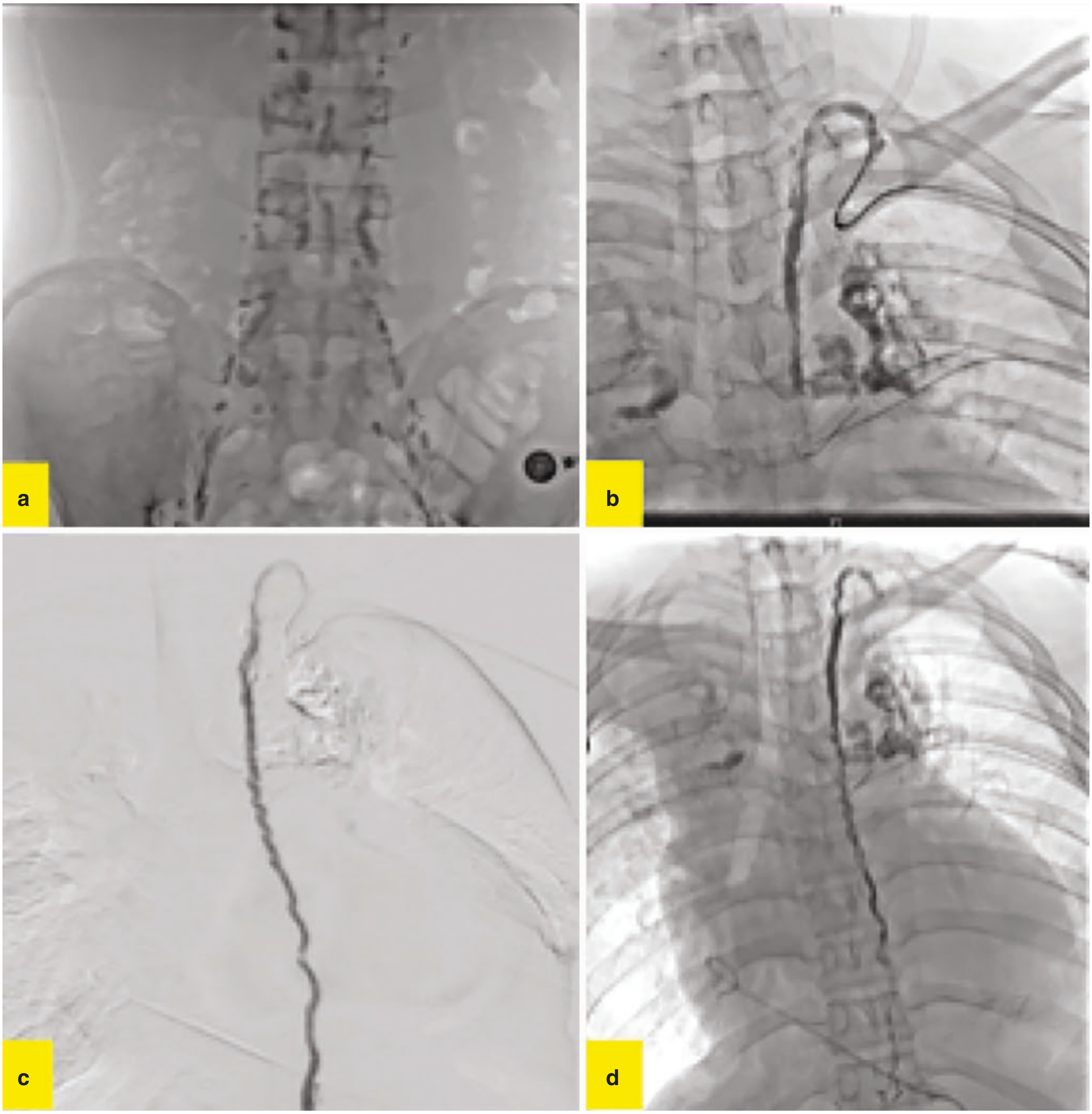


Fig. 17 (**a**) Lymphangiogram after injecting lipiodol into inguinal LN. (**b**) Transvenous cannulation of the thoracic duct. (**c**) Thoracic duct angiogram. (**d**) Post glue embolization of thoracic duct

11 Emergencies

Situations in which urgent or emergency interventional radiology is indicated are presented in Fig. 18.

11.1 Vascular Intervention

Arterial intervention: Embolization of hemorrhage, especially postoperative bleeding, tumoral bleeding (hypervascular tumors, infiltration of vessels), bleeding from the gastrointestinal tract, urinary tract, airways, and head and neck.

Venous intervention: Insertion of IVC filter, mechanical pulmonary thrombectomy.

11.2 Gastrointestinal Bleeding

GI bleeding is conventionally categorized by the anatomical location of the bleeding source (Table 4). A gastrointestinal (GI) bleeding source proximal to the ligament of Treitz,

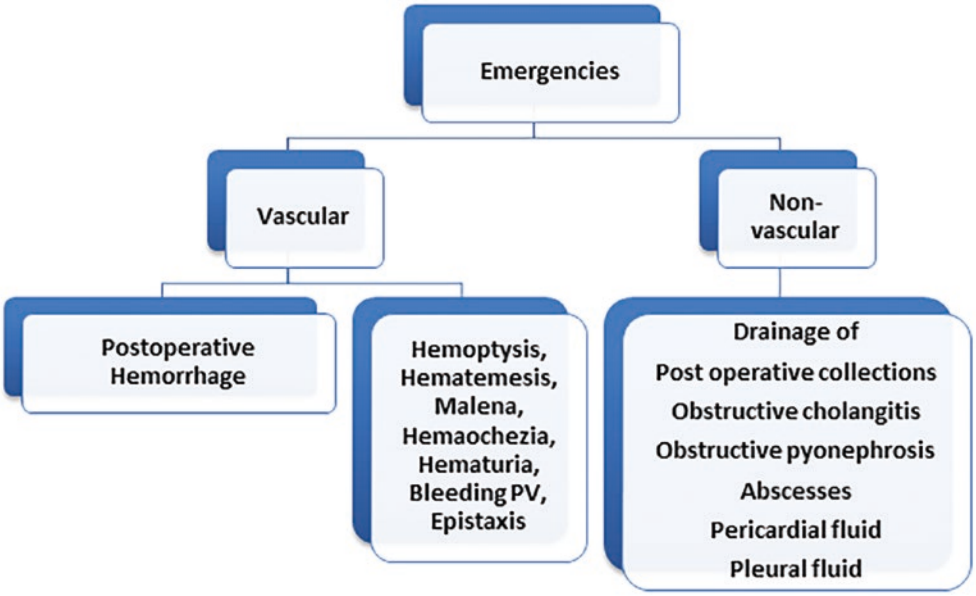

Emergencies
Vascular
Non-vascular
Postoperative Hemorrhage
Hemoptysis, Hematemesis, Malena, Hemaochezia, Hematuria, Bleeding PV, Epistaxis
Drainage of
Post operative collections
Obstructive cholangitis
Obstructive pyonephrosis
Abscesses
Pericardial fluid
Pleural fluid

Fig. 18 Situations in which urgent or emergency interventional radiology is indicated

Table 4 Gastrointestinal bleeding

Features	Upper GI bleed	Lower GI bleed
Site	Above ligament of Trietz	Below ligament of Trietz
Presentation	Hematemesis or melena	Hematochezia
Nasogastric aspiration	Blood	Clear fluid
BUN/creatinine ratio	Increased	Normal
Bowel sounds	Hyperactive	Normal

which occurs more frequently, is classified as part of upper GI, and a source distal to the ligament of Treitz is considered part of lower GI [48–50].

11.2.1 Causes of Upper GI Bleeding

Malignancy (vascular tumors, ulcerative lesions, tumors that are infiltrating into blood vessels), peptic ulcer, varices, gastritis, and duodenitis.

11.2.2 Causes of Lower GI Bleeding

Colorectal carcinoma or other pelvic tumors infiltrating the rectum or colon, inflammatory bowel disease, and diverticulosis.

11.2.3 Evaluation of the Patient with Bleed (Fig. 19)

- History: hematemesis, melena, hematochezia, and anticoagulants.
- Examination: vitals, signs of chronic liver disease.
- If hemodynamically unstable—resuscitate with IV fluids and blood products.

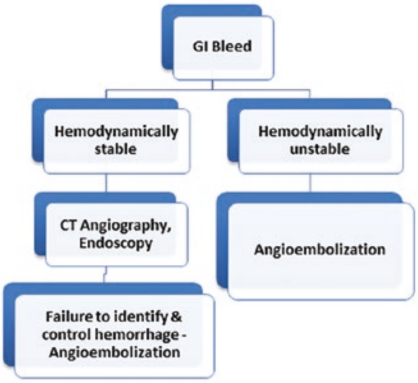

GI Bleed
Hemodynamically stable
Hemodynamically unstable
CT Angiography, Endoscopy
Angioembolization
Failure to identify & control hemorrhage - Angioembolization

Fig. 19 Approach to a patient presenting with gastrointestinal hemorrhage

- Laboratory tests: hemoglobin, platelets, coagulation profile, LFT, and RFT.

Angioembolization

- Angiography can identify an active bleeding rate of at least 0.5–1 mL/min.
- Femoral access is taken, and a mesenteric angiogram is performed.
- Superselective angiograms of the suspected vessels as guided by clinical details and prior imaging is done, and this is followed by embolization of the abnormal vessels identified to be the cause of bleeding (Fig. 20a–d).
- Augmentation maneuvers:
  - Selective intra-arterial injection of nimodipine, papaverine, and heparin.
  - Withholding of vasopressor supports for some time to unmask bleeding vessel.

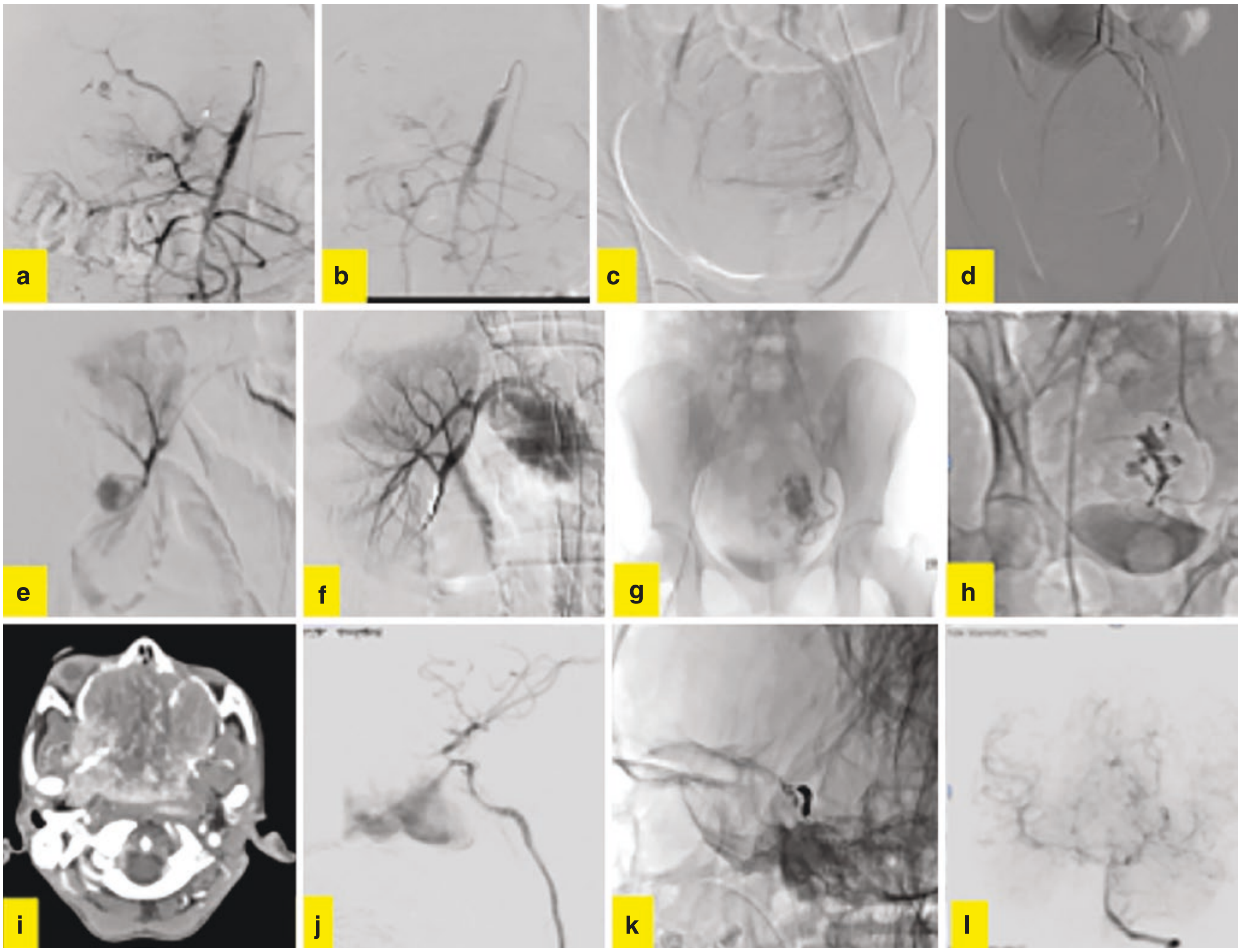


Fig. 20 (**a**) Postoperative hematemesis, SMA angiogram showing pseudoaneurysm. (**b**) SMA angiogram post glue embolization. (**c**) C/o hematochezia, left superior rectal artery angiogram showing pseudoaneurysm. (**d**) Post-embolization angiogram. (**e**) C/o post-PCN hematuria, right renal artery angiogram showing pseudoaneurysm. (**f**) Post coil embolization angiogram. (**g**) Bleeding PV in a c/o invasive mole, left uterine artery angiogram. (**h**) Glue embolization. (**i**) CECT in c/o JNA. (**j**) Postoperative right ICA blowout. (**k**) Coil embolization. (**l**) Contralateral angiogram showing support from contralateral arteries

Positive Findings

- Extravasation of contrast agent is indicative of active bleeding.
- Mucosal blushes with abnormal vessels suggestive of a tumor.
- Prolonged contrast spots suggestive of inflammation.
- Visualization of nidus with early draining vein suggestive of an AV malformation.
- Other lesions—pseudoaneurysms and AV fistulas [51, 52].

11.2.4 Complications

- Nontarget embolization.
- Bowel ischemia: avoid nontarget embolization to prevent bowel ischemia. The patient has to be monitored post-procedure clinically and with serum lactates for bowel ischemia, which would require surgery and resection of the ischemic segment of the bowel.
- An arterial injury such as dissection, perforation, pseudoaneurysm, and vasospasm [53].

11.3 Hemoptysis and Bronchial Artery Embolization

Hemoptysis is defined as the coughing up of blood originating from the lower respiratory tract. Patients with massive hemoptysis (>300 mL in 24 h) have high mortality primarily due to the risk of aspiration and asphyxiation.

Oncologic causes of hemoptysis include primary or metastatic pulmonary malignancy or infections due to post chemotherapy-related infection. Other causes of hemoptysis include tuberculosis, fungal infections, abscess, bronchiectasis, pneumonia, and chronic bronchitis. Ninety percent of cases of massive hemoptysis requiring intervention originate from the bronchial arteries [54].

11.3.1 Pre-procedural Imaging and Endovascular Treatment

CT angiography is the diagnostic modality of choice for assessing and characterizing hemoptysis. It identifies the cause of the bleed, localizes the site, and provides a vascular road map for endovascular intervention. Hypertrophy of the bronchial artery (diameter >3 mm), in conjunction with other imaging findings, improves the sensitivity and specificity of localization of the bleeding source [55, 56]. The target artery is selectively cannulated and embolized using particles.

11.3.2 Outcomes

Technical success is more than 90%, while clinical success ranges from 73% to 94%. Recurrence rates are high if the underlying disease (example: tuberculosis, bronchiectasis) is left untreated.

11.3.3 Complications

Post-embolization syndrome resulting in pleuritic pain, fever, dysphagia, and leukocytosis can occasionally occur and last for 5–7 days. Paraplegia, an unusual and the most dreaded complication of bronchial artery embolization, occurs when the spinal artery arising from the bronchial artery is not identified, resulting in inadvertent embolization of this artery.

11.3.4 Management of Hematuria and Bleeding per Vaginum

The basic patient preparation, intra-procedural care, and angiographic techniques are the same as described above. For hematuria, renal and bilateral internal iliac artery angiograms are taken depending on whether the source of bleeding is kidney or bladder/prostate. For bleeding PV, bilateral internal iliac artery and selective uterine/cervical artery cannulation are performed. Endovascular treatment should always be considered as the first option to control bleeding over hysterectomy. Embolization is performed after super selectively cannulating the culprit artery (Fig. 21e–h).

11.3.5 Management of Postoperative Hemorrhage

Postoperative bleeding is sometimes encountered due to pseudoaneurysms at the site of the ligated vessel, pseudoaneurysm formation due to postoperative inflammation/infection, and slippage of ligature from vessels. It is challenging to re-explore the patient for bleeding as postoperative changes and adhesions make it difficult to identify the bleeding source and add to the morbidity of a second open surgery. Digital subtraction angiography plays a vital role in such patients by identifying the abnormal bleeding sources and embolization of the same (Fig. 20a, b, i–l).

11.3.6 Management of Deep Venous Thrombosis and Pulmonary Thromboembolism

Acute deep venous thrombosis (DVT) is rising and particularly high in postoperative and cancer patients. Anticoagulation is the mainstay of DVT therapy to prevent DVT progression and pulmonary thromboembolism (PE) [57, 58].

Indications for catheter-directed thrombolysis for DVT [59, 60]:

- Acute limb-threatening circulatory compromise.
- Extensive IVC thrombosis (high risk of fatal PE).
- Acute renal failure from thrombus extension into renal veins.
- Clinical or anatomic progression of DVT while on anticoagulant therapy.

Indications for catheter-directed thrombolysis/thromboaspiration for PE:

- Acute massive PE presenting with shock, hypotension (SBP <90 mmHg), or other signs of systemic hypoperfusion.
- Patients with submassive PE with right ventricular dysfunction (RV strain on 2D Echo, raised cardiac enzymes, RV: LV ratio > 1).

Contraindications for catheter-directed thrombolysis:

- Active bleeding
- Recent (<10 days) major surgery, trauma, CPR
- Severe liver dysfunction
- Recent intracranial hemorrhage (<6 months)
- Bacterial endocarditis
- Intracranial tumor

Such patients can safely undergo mechanical thrombectomy/thromboaspiration.

11.3.7 Procedure

Femoral (preferably) or jugular venous access is taken. The catheter guidewire combination is advanced into the main pulmonary artery, and a long sheath is placed over the stiff wire. An angiogram is taken. The aspiration catheter is subsequently navigated to the site of thrombus in the pulmonary arteries, followed by suctioning via tubing attached to the suction pump. Serial angiograms are performed to look for residual thrombus and guide further thromboaspiration

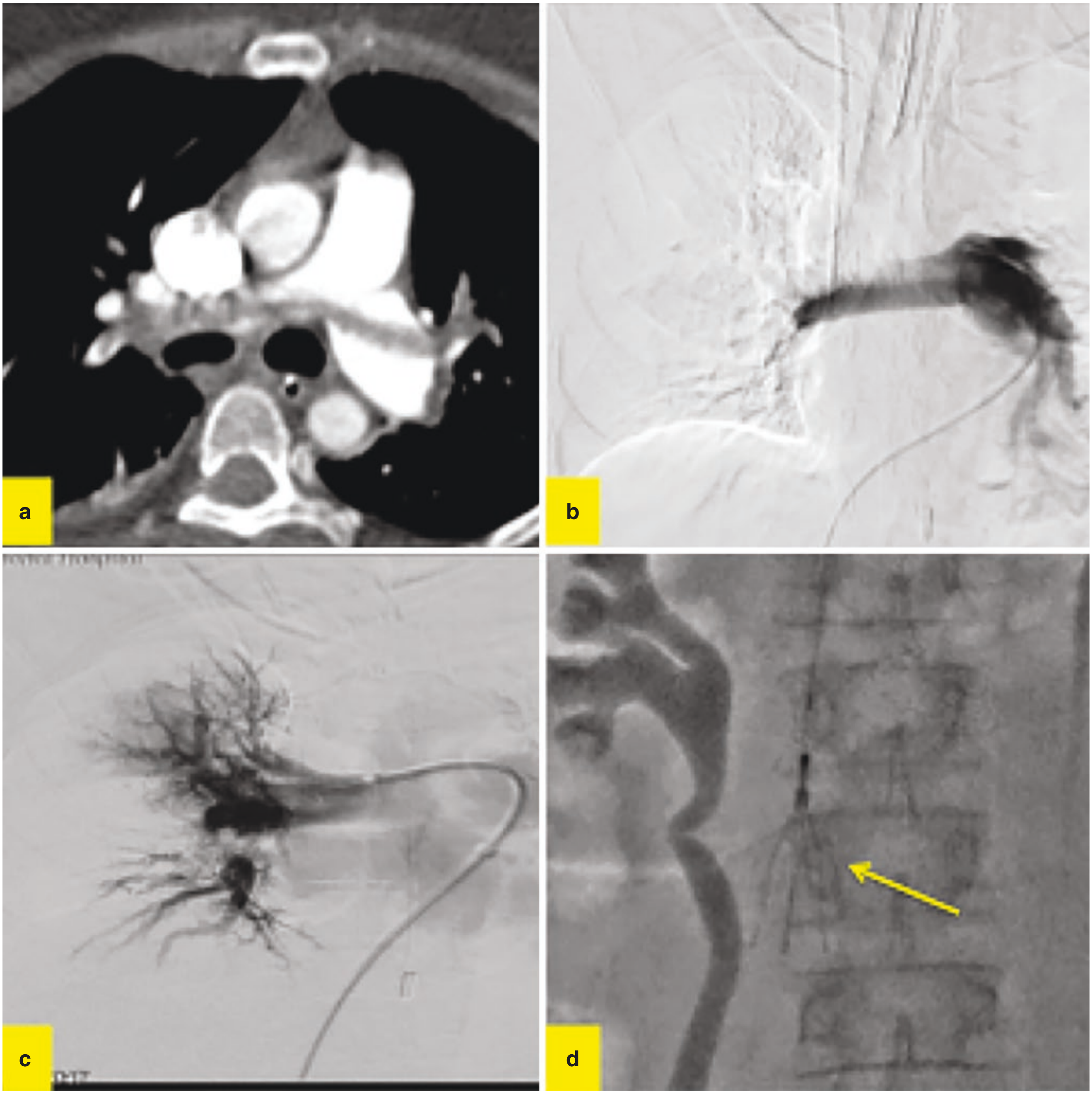


Fig. 21 (**a**) Pulmonary thromboembolism in a c/o DVT. (**b**) MPA angiogram. (**c**) MPA angiogram post thromboaspiration. (**d**) IVC filter

(Fig. 21a–c). Thrombolysis is done with urokinase or r-TPA after calculating the dose per the patient's weight and ruling out any contraindications.

A filter device (Fig. 21d) is deployed in the IVC after pulmonary thromboaspiration in patients with residual DVT to prevent further PE. The filter can be temporary (retrievable) or permanent depending on the intent of treatment and expected survival of the patient, with permanent filters being preferred in patients with the palliative intent of therapy.

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Anaesthesia in Oncology

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and J. V. Divatia

Abbreviations

ABG	Arterial blood gas
ACC	American College of Cardiology
ACS	Acute coronary syndrome
BMS	Bare metal stent
CO_2	Carbon dioxide
CPET	Cardiopulmonary exercise test
CT	Computerised tomography
CXR	Chest X-ray
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
DLCO	Diffusing capacity for carbon monoxide
DLT	Double lumen tubes
EBB	Endobronchial blockers
ER	Enhanced recovery
ESA	Erythropoiesis-stimulating agents
FiO2	Fraction of inspired oxygen concentration
GDFT	Goal-directed fluid therapy
HIPEC	Hyperthermic intra-peritoneal chemotherapy
HITHOC	Hyperthermic intra-thoracic chemotherapy
IHD	Ischaemic heart disease
IV	Intravenous
MACE	Major adverse cardiac events
MI	Myocardial infarction
NdYAG	Neodymium-doped yttrium aluminum garnet
NICE	National institute of Clinical Excellence guidelines
NMDA	*N*-methyl-D-aspartate
O_2	Oxygen
PBM	Patient blood management
PCI	Percutaneous coronary intervention
PEEP	Positive end expiratory pressure
PFT	Pulmonary function test
PO	Per-oral
SBP	Systolic blood pressure
TIVA	Total intravenous anaesthesia
VO_2	O_2 consumption
VTE	Venous thromboembolism
WHO	World Health Organisation

1 Introduction

The World Health Organisation (WHO) reports cancer as the second leading cause of death globally and was responsible for 8.8 million deaths in 2015. Approximately 70% of deaths from cancer occur in low- and middle-income countries (www.who.int/en/news-room/fact-sheets/detail/cancer). About 60–80% of these patients may need surgery for various indications ranging from diagnostic, therapeutic or palliative procedures. Most of the top ten cancers in India responsible for disability in 2016 [stomach (9.0% of the total cancer disability-adjusted Life years), breast (8.2%), lung (7.5%), lip and oral cavity (7.2%), pharynx other than nasopharynx (6.8%), colon and rectum (5.8%), leukaemia (5.2%), cervical (5.2%), oesophageal (4.3%) and brain and nervous system (3.5%)] require surgical treatment [1].

Neo-adjuvant chemotherapy is widely practiced for several cancers, and cancer patients may have undergone received chemotherapy (including newer agents for targeted therapy) and/or radiotherapy with implications for anaesthetic management. Surgical advances have resulted in both highly complex and invasive procedures (e.g. cytoreductive surgery, hyperthermic intraperitoneal chemotherapy) as well as minimally invasive procedures (e.g., robotic surgery) gaining popularity. Patients are often elderly, with several comorbidities. Perioperative management of these patients should focus on safe anaesthesia as well as optimising postoperative surgical outcomes. Oncoanaesthesia refers to the practice and study of

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anaesthetic techniques and perioperative interventions that can help facilitate early return to intended oncological treatment and potentially minimise cancer recurrence and improve oncological outcomes. This chapter will provide a brief overview of the perioperative care of cancer patients.

2 Preoperative Chemotherapy

Chemotherapeutic drugs effects can range from mild to severe adverse effects. Most of these drugs affect the gastrointestinal and haemopoieitic system. Gastrointestinal toxicity results in nausea and vomiting, mucositis and diarrhea and electrolyte disturbances. If urgent/emergency surgery is indicated in patients undergoing chemotherapy with GI manifestations, then fluid balance and electrolytes should be optimised before surgery. Care should be taken during laryngoscopy as trauma can exacerbate the mucositis and cause severe bleeding leading to difficult visualisation of the airway.

Myelosuppression is usually partially or completely reversible within 6 weeks of cessation of chemotherapy. Long duration of neutropenia was identified as one of the predictors of overall survival in these patients; therefore, surgery should be delayed, when possible, to allow for neutrophil recovery. Preoperative administration of granulocyte colony-stimulating factors (GCSF) may be considered in these cases to expedite reaching this threshold. It is prudent to order a complete blood count before elective surgery [2, 3]. Elective surgery is planned after recovery of myelosuppression. Incidental surgery may be needed for neutropenic enterocolitis, small bowel obstruction and perforative peritonitis before recovery of myelosupppression. In these cases, there can be increased risk of bleeding and opportunistic infection if the platelet count is low (<50,000/cmm) and absolute neutrophil count is less than 1000/cmm, respectively.

Certain drugs affecting various organ-specific toxicities and the clinical implications are outlined in Table 1.

Table 1 Chemotherapeutic agents, organ toxicity, mechanism of action, presentation and clinical implication for preoperative assessment and evaluation

Organ involved	Drug	Mechanism of organ toxicity	Clinical manifestation	Clinical implication
Cardiovascular	Anthracyclines [4] • Doxorubicin • Daunomycin • Idarubicin • Epirubicin Cisplatin Pentotastin Ifosfamide Cladiribine Mitoxantrone	Permanent structural changes (Type 1) in the cardiac myocyte, which worsen with repeated doses, i.e. cumulative effect.	Cardiac toxicity may be life threatening or with significant morbidities. They can be immediate or delayed after completion of the course of chemotherapy. They can range from hypotension, hypertension, arrhythmias, myocardial infarction, congestive cardiac failure, cardiomyopathy, myocarditis, and pericarditis, leading to pericardial effusion and cardiac tamponade.	• Focused history and examination, for signs and symptoms of cardiac dysfunction should be elicited. • Electrocardiogram and 2D echocardiogram (Echo) should be requested. Echo should focus on myocardial contractility, left ventricular ejection fraction, and pericardial fluid. • Asymptomatic patients with minimal or no echocardiographic changes indicative of cardiomyopathy may show subclinical cardiac dysfunction, which is only seen as a diminished ability to exercise. • For agents with cumulative effect, Echo is required before surgical procedure even years after chemotherapy. • Cardiology referral may be needed for preoperative optimisation. • Intravenous induction agents have an exaggerated myocardial depressant effect even in patients with apparently normal cardiac function. Dose titration to clinical effect is prudent. • Invasive arterial pressure and cardiac output monitoring may be needed depending on the cardiac morbidity and surgical procedure.
	Tyrosine kinase inhibitors— • Sunitinib • Imatinib • Sorafenib • Lapatinib • Dasatinib Monoclonal antibody • Trastuzumab • Bevacizumab	Type 2 changes in cardiac myocyte, which are reversible despite repeated doses.	Cause hypertension and congestive heart failure, which may be associated with elevated troponin levels. Bevacizumab can also cause severe thromboembolic events.	
	Cyclophosphamide	Direct endothelial damage.	Haemorrhagic pericarditis or myocarditis. Incidence of cardiotoxicity is lower in children than in adults, due to an age-related resistance as well as the lower doses administered to children.	

Table 1 (continued)

Organ involved	Drug	Mechanism of organ toxicity	Clinical manifestation	Clinical implication
Renal	Platinum-based [5] • Cisplatin • Carboplatin • Oxaliplatin	Renal tubular and glomerular damage.	They can cause either acute or chronic renal failure.	• Nephrotoxicity is compounded by dehydration and concurrent use of non-steroidal anti-inflammatory drugs. • Careful fluid optimisation and analgesic use during the perioperative period.
	Ifosfamide	Proximal tubular abnormality.		
	Cyclophosphamide	Haemorrhagic cystitis.		
	Mitomycin C	Syndrome encompassing microangiopathic haemolytic anaemia and renal failure.		
Respiratory	Bleomycin [6]	6–10% incidence of pulmonary toxicity. Oxidative damage, Relative deficiency of deactivating enzyme bleomycin hydroxylase, genetic susceptibility and presence of inflammatory cytokines are predisposing factors. High inspired oxygen concentrations can cause rapid progression of pulmonary toxicity.	Can be fatal. Diagnosis of bleomycin induced lung injury is established by a combination of clinical presentation, respiratory function abnormalities, radiological and histological features. Common symptoms are exertional dyspnoea and non-productive cough, which can progress to dyspnoea at rest, tachypnoea and cyanosis. Can occur during treatment or within first 6 months of treatment.	• Investigations required may include a CXR, ABG, CT chest PFT and DLCO. • Lowest FiO$_2$ should be administered to achieve a target range of SpO$_2$ between 88% and 92%. • If oxygen saturations are higher than this, then oxygen should be stopped or the dose reduced. Protective lung ventilator strategy using PEEP and careful fluid balance. • Postoperatively, chest physiotherapy, good analgesic regimes, and early mobilisation. Pulmonary toxicity is a lifelong risk in these patients so exposure to high concentrations of O$_2$ should be limited.
Nervous system	Vincristine [3]	Inhibits microtubule formation and DNA/RNA synthesis.	Peripheral neuropathy, muscle pain, cranial neuropathy, autonomic neuropathy, and in severe cases seizures. Autonomic neuropathy is a major concern for anaesthetists. Neurotoxicity is usually reversible on interruption of the therapy, but the recovery is slow and takes several months.	• Regional anaesthesia is relatively contraindicated in any patient demonstrating neurological side-effects after chemotherapy treatment and if essential it should be attempted after thorough neurological examination and documentation of deficit.
	Cisplatin Paclitaxel Oxaliplatin	Causes DNA damage-induced apoptosis of dorsal root ganglion neurons.	Most commonly presents as distal dose-dependent symmetrical sensory neuropathy.	
	High-dose methotrexate [7]	Possibly disruption of central nervous system folate homeostasis and/or direct neuronal damage.	Present with transient stroke-like symptoms, encephalopathy, seizures (usually reversible).	
	Ifosfamide [8]	Not known.	Causes metabolic encephalopathy of varying severity. Neurotoxicity is self-limiting and reversible between 48 and 72 h after discontinuation of ifosfamide.	

CXR chest X-ray, *ABG* arterial blood gas, *CT* computerized tomography, *PFT* pulmonary function test, *DLCO* diffusing capacity for carbon monoxide, FiO_2 fraction of inspired oxygen concentration

3 Preoperative Radiotherapy

Radiotherapy is frequently used in combination with chemotherapy for oesophageal, pulmonary, cervical, head and neck, rectal and urinary bladder cancers. Radiotherapy causes tissue damage along its path via production of oxygen-free radicals. Superficial tissues are maximally affected compared to deeper tissues. Side effects depend on the area affected. It causes delayed wound healing, induration of the skin, vascular stenosis, myocarditis, pneumonitis and pulmonary fibrosis. Head and neck cancers present as challenge to the anaesthetists, especially in airway management. Induration of the tissues may result in limited neck extension, restricted mouth opening, tongue mobility and rigidity and oedema of the oropharyngeal tissues. This may make facemask ventilation and laryngoscopy difficult. The anaesthetist has to be prepared with airway management plan and extubation strategy.

4 Perioperative Care

Perioperative care is a continuum of care, starting from the preoperative evaluation, intraoperative management and postoperative care (Fig. 1). Optimal perioperative care is essential for good short-term outcomes as well as long-term outcomes.

The aim of the preoperative evaluation is to identify the high-risk patient (Table 2) and to optimise pre-existing medical conditions. Appropriate specialist referral and consultation should take place on an individualised basis.

Several corrective problems must be identified and treated. These include malnutrition, anaemia, ischaemic heart disease (IHD), diabetes mellitus, pulmonary disease and optimisation of fluid volume to reduce the incidence renal dysfunction.

Table 2 Identifying the high-risk patient for cancer surgery

Patient factors	Surgical factors
• Prior severe cardiac illness (acute myocardial infarction, stroke, congestive heart failure) • Age >70 years, limited physiologic reserve of ≥1 organs • Sepsis and with septic shock • Severe nutritional problems • Respiratory distress, chronic obstructive pulmonary disease, patient requiring mechanical ventilation • Hepatic or renal dysfunction	• Extensive ablative surgery for cancer, >8 h • Massive blood loss >8 units • Vascular surgery • Acute abdominal catastrophe-peritonitis, perforated bowel with gangrene

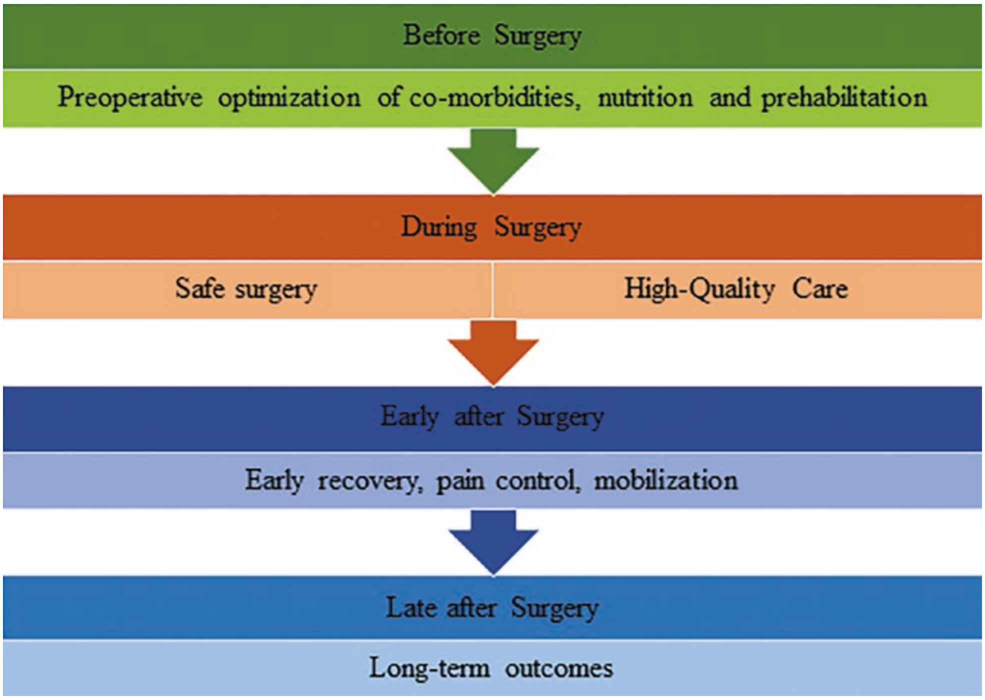

Before Surgery
Preoperative optimization of co-morbidities, nutrition and prehabilitation
During Surgery
Safe surgery
High-Quality Care
Early after Surgery
Early recovery, pain control, mobilization
Late after Surgery
Long-term outcomes

Fig. 1 The continuum of perioperative care

5 Cardiovascular Evaluation in Patients Undergoing Oncologic Surgery

With improved access to healthcare, there is growing population of elderly with multiple comorbidities, especially IHD. Cardiovascular evaluation is an important aspect of pre-anaesthetic assessment. Most oncologic surgical procedures are classified as time sensitive, i.e. a delay of >1–6 weeks can be allowed for evaluation and significant changes in management will negatively affect outcome. Prior cardiac events such as recent myocardial infarction (MI) are often associated with major adverse cardiac events (MACE); their timing and stability have an impact on the perioperative morbidity and mortality. As the duration between onset of MI and timing of surgery increases the incidence of postoperative MI and mortality decreases from 32% and 14% within 1 month to 5.9% and 10% at 6 months after MI, respectively [9]. According to the American College of Cardiology (ACC)/American Heart Association (AHA)/guidelines at least 2 months should elapse after MI before non-cardiac surgery in the absence of a coronary intervention. In addition to cardiac morbidity and mortality, recent MI (within 6 months of non-cardiac surgery) is associated with increased risk of perioperative stroke and an eightfold increase in mortality [10]. Patients having three or more of the following risk factors have a >10% chance of suffering a MACE: high-risk surgical procedure (intrathoracic, intraperitoneal or supra-inguinal vascular reconstruction); history of IHD (excluding revascularisation); history of congestive cardiac failure; history of stroke or transient ischaemic attack; insulin-dependent diabetes mellitus; preoperative insulin therapy (diabetes) and creatinine >2.0 mg% [11].

The ACC/AHA recommendations for preoperative evaluation of patients with IHD are summarised in Fig. 2.

Cardiopulmonary exercise test (CPET) is a non-invasive procedure that involves the measurement of expired ventilation, oxygen (O_2) consumption and carbon dioxide (CO_2) production during incremental exercise. It may be superior to standard ECG stress testing in detecting both overt and occult exercise-induced myocardial ischaemia. Maximal increase in O_2 consumption (VO_2) with exercise (peak VO_2) < 15 mL/kg and anaerobic threshold <10 mL O_2/kg/min are associated with poor postoperative outcome.

Revascularisation (coronary artery bypass graft surgery or percutaneous coronary intervention [PCI]) is not recommended before non-cardiac surgery exclusively to reduce perioperative cardiac events. Indication for revascularisation depends on severity of IHD, rather than impending surgery. In patients who have had PCI, the immediate period after a PCI is a high-risk period because of the rupture of its endothelial covering. Non-cardiac surgery is risky till epithelialisation, with a high rate of AMI (up to 30%) and mortality (20–40%). Dual antiplatelet therapy (DAPT) with aspirin and $P2Y_{12}$ platelet receptor–inhibitor (e.g., clopidogrel) is mandatory to prevent in-stent thrombosis. Discontinuation of DAPT following PCI is one of the strongest predictors of stent thrombosis. The risk of stent thrombosis and mortality is inversely proportional to the timing of surgical procedure. The new generation drug eluting stents (DES) are associated with a lower risk of stent thrombosis and require a shorter minimum duration of DAPT. Current recommendation for discontinuation DAPT before elective non-cardiac surgery for bare metal stent (BMS) is >30 days after implantation and 3–6 months for DES (if the risk of delaying surgery is greater than risk of stent thrombosis). Safe duration for discontinuation of DAPT for DES is 6 months after implantation [12]. Continuation of DAPT is associated with increased bleeding risk during surgery. The decision to continue or withhold DAPT should be individualised depending on the urgency of non-cardiac surgery. If decision to discontinue clopidogrel is taken, then aspirin should be continued perioperatively and $P2Y_{12}$ platelet receptor–inhibitor should be restarted as soon as possible after surgery [13].

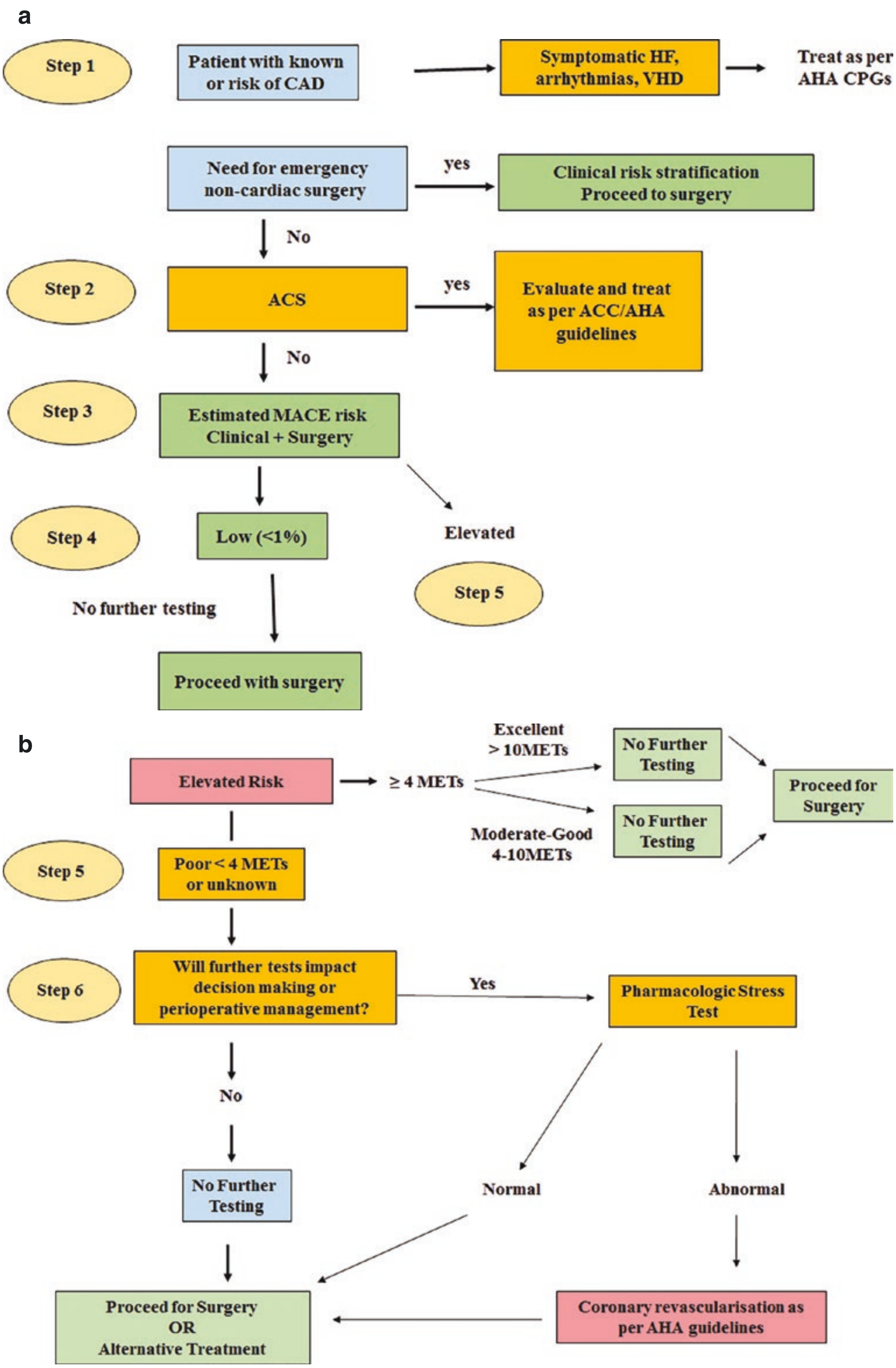

a
Step 1
Patient with known or risk of CAD
Symptomatic HF, arrhythmias, VHD
Treat as per AHA CPGs
Need for emergency non-cardiac surgery
yes
Clinical risk stratification Proceed to surgery
No
Step 2
ACS
yes
Evaluate and treat as per ACC/AHA guidelines
No
Step 3
Estimated MACE risk Clinical + Surgery
Step 4
Low (<1%)
Elevated
Step 5
No further testing
Proceed with surgery
b
Excellent > 10METs
No Further Testing
Elevated Risk
≥ 4 METs
Proceed for Surgery
Moderate-Good 4-10METs
No Further Testing
Step 5
Poor < 4 METs or unknown
Step 6
Will further tests impact decision making or perioperative management?
Yes
Pharmacologic Stress Test
No
No Further Testing
Normal
Abnormal
Proceed for Surgery OR Alternative Treatment
Coronary revascularisation as per AHA guidelines

Fig. 2 (**a**, **b**) Stepwise approach for management of patients with risk factors for coronary artery disease (CAD). *ACS* acute coronary syndrome, *HF* heart failure, *VHD* valvular heart disease, *CPG* clinical practice guidelines by ACC/AHA, *METs* metabolic equivalents

6 Frailty and Anaesthesia

Elderly patients undergoing surgical procedures are more vulnerable to adverse postoperative outcomes compared to younger patients. Functional status, gait and mobility and frailty are important determinants of outcome [14]. Frailty is a state of reduced physiological reserve as a result of long-term illness, multiple comorbidities leading to progressive decline in physical and cognitive function. These patients will have loss of muscle mass, reduced strength and endurance. Frailty is associated with worse postoperative

Table 3 Screening for frailty [15]

Criteria	Definition
Shrinkage	Unintentional weight loss ≥10 lb over the past year
Weakness	Decreased grip strength
Exhaustion	Self-reported poor energy and endurance
Low physical activity	Low weekly energy expenditure
Slowness	Slow walking

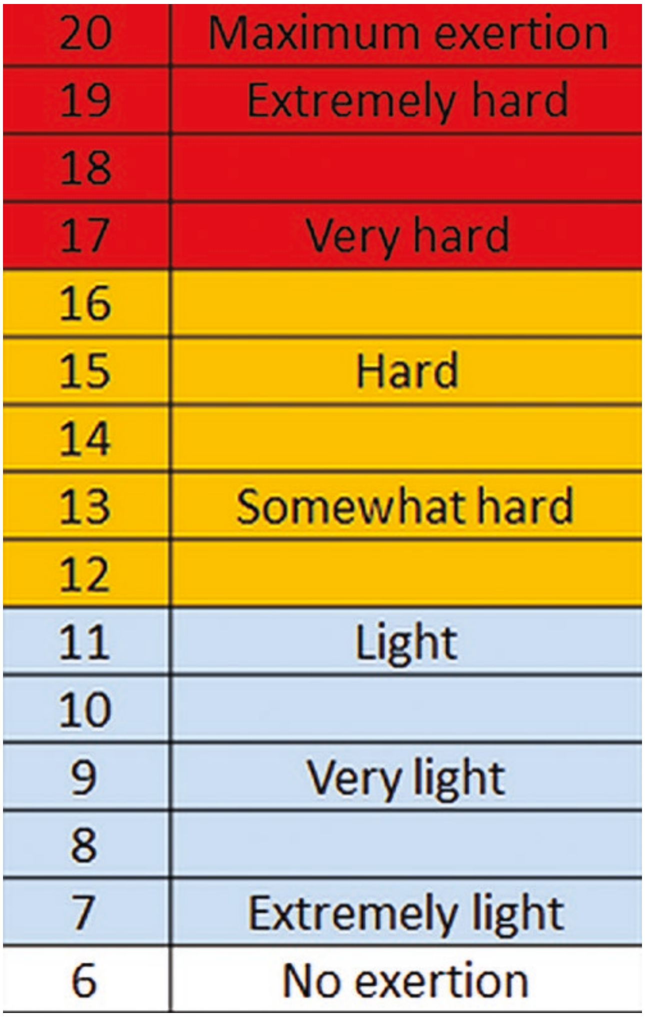
1 point for each criterion met
0–1: Not frail; 2–3: Intermediate frail (pre-frail); 4–5: Frail

outcomes such as increased postoperative complications, prolonged stay and mortality. Elderly patients are more prone to postoperative delirium and postoperative cognitive dysfunction.

Preoperative interventions such as prehabilitation can be initiated to improve muscle strength, mass and thus physical function [15]. Similarly, improving nutrition, physiotherapy, screening for cognitive disorder, treatment of depression or mood disorders if any. During anaesthesia, in addition to other aspects of anaesthetic care particular attention is needed to maintain normothermia, avoidance of fluid overload, titrate depth of anaesthesia to avoid deep levels of anaesthesia, as it is associated postoperative delirium and cognitive decline. Lastly, frailty should be assessed and incorporated in to decision-making process taking in to consideration its association with worse postoperative outcomes (Table 3).

7 Prehabilitation

Prehabilitation is a proactive approach of involving patients actively in their care. There is ample evidence that prehabilitation improves outcomes early return of functional status [16–18]. The aim is to provide structured, individualised exercise regime to improve cardiorespiratory fitness and muscular conditioning. The exact mechanism is unclear, but it seems that a trained fit patient is better adept to deal with perioperative stress and sequelae. A multimodal strategy is superior to single modality in terms of functional recovery [17]. Taking into consideration of time sensitivity of an oncologic surgery, there a relative short window of opportunity to prehabilitation and optimisation of the patient. Prehabilitation has four components, such as medical optimisation, physical exercise and nutritional and psychological support. Medical intervention consists of optimisation of the co-morbidities such as hypertension, diabetes, asthma, management of anaemia etc.



20	Maximum exertion
19	Extremely hard
18	
17	Very hard
16	
15	Hard
14	
13	Somewhat hard
12	
11	Light
10	
9	Very light
8	
7	Extremely light
6	No exertion

Fig. 3 Borg scale of perceived exertion following exercise

Patients are encouraged to exercise. A baseline assessment of functional capacity is performed using CPET and the 6-min walk test. The exercise regime consists of 3–5 sessions per week of 30–60 min including a warm up and cool down time. Exercise typically prescribed is strength and aerobic training as cardiorespiratory fitness decrease in the postoperative period. The Borg scale of perceived exertion is a subjective tool often used during exercise testing and training to estimate effort based on how strenuous the exercise feels (Fig. 3). The target is typically in the range of 12–16.

The goal of nutrition support is to optimise nutrient stores preoperatively and provide adequate nutrition to compensate for the catabolic response of surgery postoperatively. Preoperative nutritional support alone or in combination with preoperative exercise training has been associated with shorter postoperative stay in colorectal surgery. The European Society for Clinical Nutrition and Metabolism recommends 1.2–1.5 g protein/kg, for surgical patients. To be successful, preoperative nutrition support requires time and should be initiated early. A window of opportunity is the time period when decision for surgery is taken until the actual surgery and extends into the postoperative period [19].

Depression has been associated with infectious complications and poor wound healing [20]. Effective psychological and cognitive interventions provide information about what the patient's perioperative experience will feel like, development of positive attitude, behavioural instruction on what can be done to improve outcome, and relaxation techniques such as hypnosis and progressive muscle relaxation [21].

8 Anaesthesia and Enhanced Recovery After Surgery (ERAS)

Enhanced recovery (ER) conglomeration of different elements of care implemented perioperatively in patients undergoing elective surgery. The aim is to optimise patient's preoperative health to the best possible state before surgery, minimise perioperative stress response during surgery, early recovery and return to normal function and early recognition of abnormal recovery and intervention if necessary. Elements of an ERAS protocol are summarised in Fig. 4.

Compliance with ER elements has been associated with reduced morbidity and length of stay and cost with no impact on readmission across various surgical procedures such as colorectal, gynaecological, urological, pancreatic and liver surgery [22–29]. Quantitative impact of compliance to ER elements has demonstrated a favourable association with reduced morbidity, mortality and length of stay when the compliance was more than 80% with ER elements in patients undergoing pancreatic cancer resections [30].

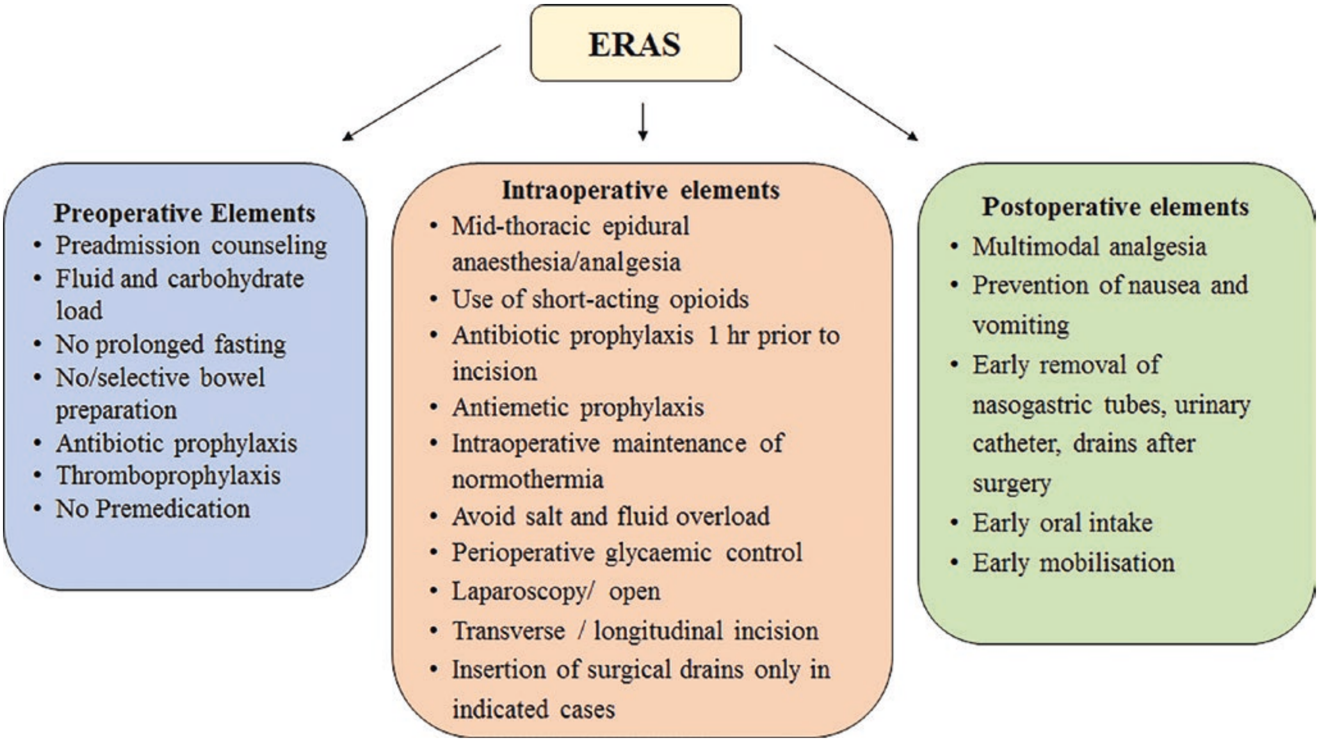

ERAS
Preoperative Elements
• Preadmission counseling
• Fluid and carbohydrate load
• No prolonged fasting
• No/selective bowel preparation
• Antibiotic prophylaxis
• Thromboprophylaxis
• No Premedication
Intraoperative elements
• Mid-thoracic epidural anaesthesia/analgesia
• Use of short-acting opioids
• Antibiotic prophylaxis 1 hr prior to incision
• Antiemetic prophylaxis
• Intraoperative maintenance of normothermia
• Avoid salt and fluid overload
• Perioperative glycaemic control
• Laparoscopy/ open
• Transverse / longitudinal incision
• Insertion of surgical drains only in indicated cases
Postoperative elements
• Multimodal analgesia
• Prevention of nausea and vomiting
• Early removal of nasogastric tubes, urinary catheter, drains after surgery
• Early oral intake
• Early mobilisation

Fig. 4 Various components of ERAS in the perioperative period

9 Patient Blood Management

The European cancer anaemia survey found a prevalence of 25% in patients with head and neck cancer and 53% in those with a haematological cancer with a haemoglobin (Hb) cut-off 12 g/dL [31]. Patient blood management (PBM) is an evidence based multimodal, multidisciplinary clinical concept. It was developed in non-oncology patients with the aim to reduce perioperative blood transfusions and improve perioperative outcomes and patient safety. It consists of early diagnosis and treatment of anaemia before surgery, minimising intraoperative blood loss and harnessing physiological tolerance of anaemia in the postoperative period. The aim is to minimize use of allogenic blood transfusion and its associated immunomodulatory effects [32] (Table 4).

Table 4 Patient blood management in the perioperative period

	Preoperative	Intraoperative	Postoperative
Diagnosis and treatment of anaemia	Identify and treat anaemia at the earliest preferably 4–6 weeks before surgery. Consider oral or IV iron for absolute/functional iron deficiency. ESA can be used if after correction of iron deficiency if Hb below 10 g%; however, caution due to 1.5-fold increased risk of VTE in cancer patients [33]. Treat any vitamin B12/folate deficiency.	Identify and treat any pre-existing bleeding disorder. Review medications (antiplatelet, anticoagulation therapy). Minimise iatrogenic blood loss, i.e. repeated blood sampling.	Early nutrition and correct anaemia. Minimise iatrogenic blood loss, i.e. repeated blood sampling. IV iron can be administered to correct iron deficiency.
Minimisation of blood loss	If possible schedule surgery after optimisation of patient's Hb.	Central neuraxial blockade (has been shown to reduce blood loss during surgery). Proper patient positioning to improve venous drainage and reduce blood loss. Meticulous haemostasis in the surgical field. Maintain normothermia, ionic calcium >1 mmol/L, avoid acidosis pH <7.2. Use of antifibrinolytics such as tranexamic acid. Use goal-directed therapy for blood and blood products as per lab and visco-elastic testing.	Monitor and manage bleeding. Minimise iatrogenic blood sampling loss.
Management of anemia tolerance	Optimise cardiac and pulmonary function. Individualise patient-specific management for appropriate blood conservation modalities.	Use restrictive transfusion threshold if patients do not have major haemorrhage, ACS or need regular blood transfusions for chronic anaemia. Consider a threshold of 7 g% and a Hb concentration target of 7–9 g% after transfusion. Consider a threshold of 8 g% and a Hb target of 8–10 g% after transfusion for patients with ACS (NICE 2018, NG24).	Adhere to transfusion thresholds.

IV intravenous, *ESA* erythropoiesis-stimulating agents, *VTE* venous thromboembolism, *ACS* acute coronary syndrome, *NICE* National institute of Clinical Excellence guidelines

10 Intraoperative Techniques that Affect Postoperative Outcome

Fluid therapy and haemodynamic monitoring Patients undergoing major surgery are at high risk of tissue hypoperfusion and organ dysfunction due to the presence of inflammatory response, hypovolaemia and increased oxygen requirement. Fluid therapy is essential to restore tissue perfusion. However, excessive fluid intake has harmful effects by causing tissue oedema and reduced perfusion and has been associated with increased morbidity and mortality. On the other hand, excessive fluid restriction may lead to reduced tissue perfusion, delayed wound healing and renal dysfunction [34]. It has been suggested that haemodynamic monitoring should be used for goal-directed fluid therapy (GDFT). Invasive arterial pressure monitoring and use of haemodynamic strategies such as optimisation of fluid responsiveness parameters, stroke volume optimisation and optimisation of oxygen supply and demand parameters have been used for GDFT. A recent meta-analysis that included data from 95 trials and 11,659 patients found that GDFT was associated with significantly reduced odds of mortality (0.66, 95% confidence interval 0.50–0.87) and also reduced odds of pneumonia, acute kidney injury, wound infection and hospital length of stay [35].

Various other techniques with potential to affect postoperative outcome are as follows:

Protective lung ventilation strategy for mechanical ventilation during surgery [5]. It consists of ventilating with tidal volume 6–8 mL/kg of predicted body weight with positive end expiratory pressure (PEEP) 6–8 cm H_2O. Recruitment manoeuvre is done every 30 min after intubation. It is associated with 60% reduced risk of major pulmonary and extrapulmonary complications within 7 days compared to non-protective ventilation strategy, reduced need for non-invasive ventilation or tracheal intubation and shortened postoperative stay.

Individualised blood pressure management strategy [5]. Walsh et al. demonstrated that mean arterial pressure (MAP) < 55 mmHg predicted adverse cardiac- and renal-related outcomes [36]. Similarly, Salmasi et al. found that MAP <65 mmHg or relative thresholds of 20% from baseline were progressively related to both myocardial and kidney injury [37]. In view of adverse effects related to hypotension, maintaining systolic blood pressure (SBP) within 10% of patient's baseline SBP is associated with significantly lower rates of postoperative organ dysfunction. Vasopressors such as norepinephrine can be used to achieve blood pressure targets.

Maintaining normothermia (temperature 36–37 °C). Hypothermia has adverse effects on coagulation and the microcirculation and is associated with wound infections, myocardial ischaemia and blood transfusions. Therefore, patients should be kept warm in theatre, the recovery room and the ward for the first 24–48 h. This is best achieved by during surgery by using a warm air blanket and using warm fluids. Core temperature (nasopharyngeal or oesophageal) must be monitored during anaesthesia.

11 Anaesthesia for Head and Neck Surgery

Head and neck surgery for cancer includes a wide spectrum of surgical interventions, ranging from short day-case procedures like diagnostic endoscopies and laser excisions to very long and complex operations involving microvascular reconstructive surgery lasting over 12 h. Head and neck surgeries pose a special challenge to the anaesthetist due to risk of potential airway compromise, shared airway with surgeons, prolonged nature of surgery and associated blood loss. The greatest challenge is control of the airway throughout the perioperative period. Primary pathology and/or treatment can make the airway difficult. Therefore, inappropriate management can jeopardise ventilation and oxygenation resulting in morbidity or mortality. Clear communication within the team perioperatively is essential for a safe and satisfactory outcome.

Patients with perilaryneal tumours may present with stridor. Mild upper airway obstruction by a laryngeal tumour is often mistaken for "bronchospasm" in the initial stages and misdiagnosed as asthma. Stridor at rest is suggestive of a reduction in airway diameter by at least half, i.e. tracheal diameter less than 6 mm in adults. Stridor that worsens on extension of the neck or on gentle downward pressure on the larynx or inability to lie supine indicates severe obstruction. A flow-volume loop helps in identifying the location of obstruction (extrathoracic or intrathoracic) and the type of obstruction (fixed or variable). It is prudent to look at the findings of the most recent indirect laryngoscopy or endoscopic examination, and be familiar with the site, size and extent of the lesion. Large intraoral tumours, as well as those involving the right border of the tongue, base of the tongue and vallecula tend to bleed during laryngoscopy attempts and can make subsequent mask ventilation and intubation difficult. Presence of ankyloglossia signifies that the tongue is fixed and may not be easily displaced during direct laryngoscopy and likely difficult intubation. Trismus is a common in patients with oral cancers. Recent onset of painful trismus due to inflammation and infection associated with tumour may resolve after induction of anaesthesia. Long-standing trismus associated with submucous fibrosis, radiation-induced fibrosis of the temperomandibular joint, and tumour infiltration of the infratemporal fossa and pterygoid muscles is often painless and unlikely to improve after administration of a muscle relaxant making the airway difficult. Awake fibreoptic intubation is the safest airway management technique in such cases.

The anatomy of the patient's airway influences the choice of induction technique. Anaesthetic and surgical management of potential supra-glottic obstruction includes following options:

- Oral/nasal endotracheal intubation by videolaryngoscopy or direct laryngoscopy.
- Inhalation induction with endotracheal intubation.
- Intravenous induction with muscle relaxant with intubation.
- Tracheostomy under local anaesthesia.
- Recent techniques like the use of high flow oxygen by nasal cannula maintain oxygen for a longer duration (about 20 min) during apnoea, increasing the safety of the procedure and allowing surgical procedures of 20–30 min duration to be performed without intubation under apnoeic conditions [38].

Majority of these resections may require reconstructive surgery with either pedicle or free tissue transfer. The guiding principle of anaesthesia for reconstructive surgery is to maintain optimum blood flow. This can be achieved as follows:

- Traditionally, the use of hypervolaemic haemodilution was recommended during anaesthesia to maintain good flap blood flow by decreasing viscosity, increasing cardiac output and avoiding vasoconstriction. However, free flaps have no lymphatic drainage thus are prone to interstitial oedema and excessive fluid administration may in fact be detrimental. Haemodilution enhances microcirculatory flow. Haematocrit below 30% does not provide any further benefit as the curve of viscosity versus haematocrit flattens off markedly. If the haematocrit falls below 24%, the marginally improved flow characteristics from a lower viscosity may then be offset by a reduction in oxygen delivery. Therefore, normovolaemia should be maintained.
- Avoiding hypothermia and hypocapnia prevents vasoconstriction. Hypocapnia increases peripheral vascular resistance and reduces cardiac output. The aim is to maintain normothermia and normocapnia.
- Isoflurane has the advantage over other volatile anaesthetics as it causes vasodilatation with minimal myocardial depression. Propofol inhibits platelet aggregation and reduces the risk of thrombosis. In experimental studies, sevoflurane has been shown to have beneficial effects on the microcirculation by decreasing extravasation of plasma into the interstitial space, and thus limiting flap oedema.

Common postoperative problems are airway compromise, airway injury, haemorrhage, pulmonary aspiration and negative pressure pulmonary oedema after relief of airway obstruction. The airway must be secured until complete recovery of reflexes and higher functions to protect the airway against obstruction and aspiration. Patients are transferred to the post anaesthesia care unit with the tracheal tube in situ and extubated when the patient is wide-awake with intact reflexes. Elective ventilation may be required in case of massive blood loss or hypothermia, till the temperature normalises, effects of all anaesthetic drugs have worn off and patients are haemodynamically stable. Tracheostomy is preferred in cases of resection of floor mouth, resection > two-thirds of tongue, when mandibular resection has crossed the midline, in presence of bulky flaps that occupy a large part of the oral cavity or if there are limited postoperative resources to manage airway problems.

12 Laser Resections for Airway Tumours

Laser resection may be used in patients with pharyngeal, tracheal or bronchial strictures or for palliation of airway tumours. Carbon dioxide (CO_2) and NdYAG (neodymium-doped yttrium aluminum garnet) lasers are commonly used. The CO_2 laser is characterised by limited tissue penetration, which restricts its use to localised lesions of the upper airway. In contrast, the NdYAG laser exhibits enhanced tissue penetration and can be transmitted through fibreoptic bronchoscope; therefore, it is much more effective for the ablation of large masses in the trachea and bronchi. The requirements during anaesthesia for laser surgery are complete patient immobility, shared airway with surgeon, un unrestricted surgical access, protection of distal airway against blood and products of vaporisation, protection of patient and staff from stray laser radiation/reflection, removal of smoke and debris and prevention of airway fires. Maintenance of airway and mode of ventilation depend upon the site of the target lesion. For laryngeal lesions, the procedure is often performed using the operating microscope. Ventilation is often possible via an endotracheal tube as in micro-laryngoscopy. When the tracheal tube interferes with the surgical resection, as with lesions of the posterior commissure, bulky lesions and in children, apnoeic oxygenation with intermittent ventilation with venturi or breathing circuit can be done.

Small-diameter, laser-resistant cuffed tubes can be used. Polyvinyl chloride tubes are readily flammable and combustion products are tissue toxic and hence should not be used in these types of surgeries. Red rubber tubes are more fire resistant and burn slowly. Wrapping these tubes with aluminium foil makes them fire resistant; however, if the laser beam gets accidentally directed onto the foil, it gets scattered and can cause damage to the surrounding normal mucosa. Endotracheal tube cuff is filled with saline/water to decrease chances of fire should the laser beam strike the cuff. Also, wet cotton pledgets are placed on the cuff by the surgeons to prevent the laser beam inadvertently striking the cuff.

It is prudent to use a gas mixture of air and oxygen instead of nitrous oxide as it supports combustion. Also inspired oxygen concentration of less than 30% should be used. In case of airway fire, the anaesthesia circuit should be immediately disconnected and the surgical site flooded with sterile normal saline. After through suctioning, the damaged tube is removed and replaced with a fresh tube. The patient is ventilated with 100% oxygen, and the damage in lower airway is assessed by fibreoptic bronchoscopy. The patient should be given steroids, humidified oxygen and supportive care.

13 Anaesthesia and Thoracic Surgery

Anaesthesia for major thoracic surgeries is highly specialised and covers a spectrum of procedures such as lung resection, oesophagectomy, chest wall tumour excision and resection of mediastinal mass. A majority of patients presenting for lung resections for malignancy are smokers and may have end-organ damage related to the effects of smoking such as chronic obstructive pulmonary disease or ischaemic heart disease. Careful risk stratification and optimisation are needed in these patients. A scheme for preoperative evaluation for lung resection surgery is depicted in Fig. 5.

In patients with mediastinal mass, careful review of the scans and discussion with the surgeons to look for involvement of major airways and vascular structures is important. Induction of general anaesthesia can precipitate airway obstruction, which is worsened by positive pressure ventilation. Airway obstruction may occur at the level of the distal trachea or main bronchus and can result in complete failure to ventilate the patient. Supraglottic devices or tracheostomy cannot salvage this situation, and rigid bronchoscopy may be the best rescue option to restore ventilation. Flow-volume loops do not help in risk stratification for severe airway obstruction, which is best done by evaluation of symptoms and the CT scan. Low-risk patients are asymptomatic and have no tracheal compression on the CT scan. High-risk patients, such as

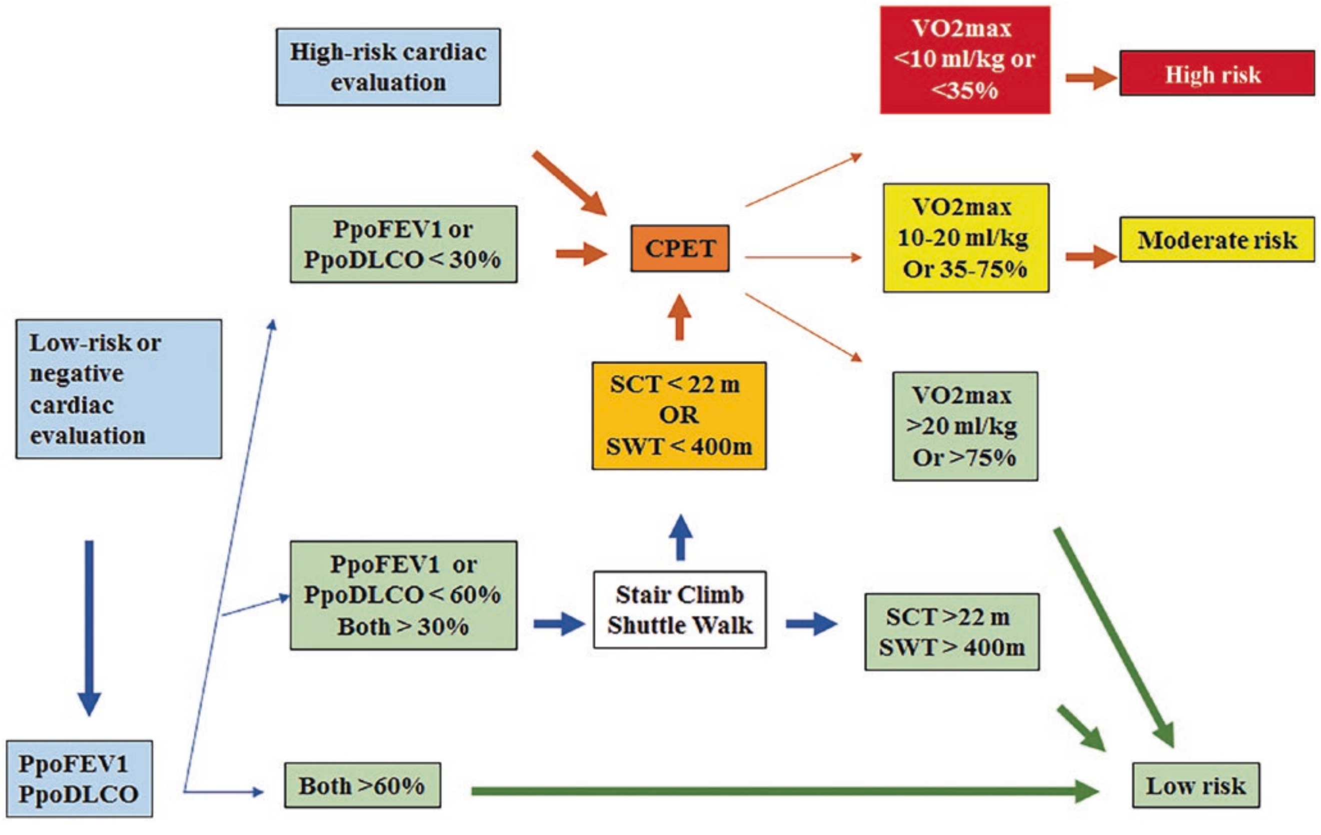

High-risk cardiac evaluation
VO2max <10 ml/kg or <35%
High risk
PpoFEV1 or PpoDLCO < 30%
CPET
VO2max 10-20 ml/kg Or 35-75%
Moderate risk
Low-risk or negative cardiac evaluation
SCT < 22 m OR SWT < 400m
VO2max >20 ml/kg Or >75%
PpoFEV1 or PpoDLCO < 60% Both > 30%
Stair Climb Shuttle Walk
SCT >22 m SWT > 400m
PpoFEV1 PpoDLCO
Both >60%
Low risk

Fig. 5 Preoperative evaluation for lung resection surgery [39]. *Ppo* predicted postoperative, *FEV1* forced expiratory volume in 1 s, *DLCO* diffusing capacity for carbon monoxide, *SCT* stair climbing test, *SWT* shuttle walk test, *VO2max* maximum oxygen consumption, *CPET* cardiopulmonary exercise test

children with >50% tracheal compression, are severely symptomatic, may present with stridor or cyanosis, severe postural symptoms, pericardial effusion or the superior vena cava syndrome. General anaesthesia should be avoided if possible, especially in high-risk cases. Spontaneous ventilation should be maintained as far as possible. If the airway obstruction is extremely severe, cannulation and preparation for cardiopulmonary bypass should be considered before induction of anaesthesia and not after total airway obstruction and severe hypoxemia have set in [40].

Certain thoracic procedures need separation of the lungs for better surgical access and for control of ventilation. The most common techniques used for lung isolation are double lumen tubes (DLT), endobronchial blockers (EBB) and endobronchial single-lumen tubes. DLTs have traditionally been considered the gold standard for lung isolation; the advantages are faster lung collapse, better quality of suctioning, lesser malposition and ability to ventilate either lung. A variety of EBBs are currently available and their advantages include less trauma, ability to offer selective lobar blockade and useful in a patient with difficult airway. Endobronchial intubation with a single lumen tube is inferior to either of the above techniques since it does not allow ventilation or suctioning of the isolated lung and should be considered only as the last option.

Collapse of the isolated lung during one-lung ventilation creates an obligatory shunt with resultant hypoxemia. Physiological techniques to overcome this hypoxemia include patient positioning (with the collapsed lung non-dependent to allow gravitational decrease in perfusion) and hypoxic pulmonary vasoconstriction. If these measures fail, introduction of ventilatory strategies like recruitment manoeuvres, application of PEEP to the ventilated lung and CPAP to the non-dependent lung should be considered. With increasing understanding of lung injury during one-lung ventilation, the emphasis is on lung protective ventilation using low tidal volumes (4–6 mL/kg predicted body weight), PEEP, recruitment manoeuvres, use of inhaled anaesthetics (sevoflurane) and lowest tolerated FiO_2. Intra-operative complications can be mainly due to hypoxemia during one-lung ventilation, bleeding from vascular injury and haemodynamic instability compounded by direct mechanical retraction of the heart or arrhythmias.

Both thoracotomy and thoracoscopy are associated with significant acute and chronic pain, which is multifactorial in aetiology and arises from rib retraction, pressure on intercostal nerves and positioning. Thoracic epidural analgesia has been considered the gold standard for thoracotomy. Paravertebral blocks have been described as an effective alternative. There is growing interest in the role of fascial plane blocks such as the erector spinae block and the serratus plane block [41].

14 Unique Onco-Surgical Procedures

Certain procedures are unique to cancer patients such as cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC), proton therapy, robotic surgery for various malignancies. These will be discussed briefly below covering main aspects of anaesthetic implications [42].

14.1 Cytoreductive Surgery with Intraoperative Chemotherapy (Hyperthermic Intraperitoneal Chemotherapy [HIPEC] and Hyperthermic Intra-thoracic Chemotherapy [HITHOC])

It involves extensive resection of visible tumour followed by direct exposure of microvascular residual disease to hyperthermic (42–45 °C) chemotherapy. Heated chemotherapy causes direct thermal injury to cancer cells in addition to immune-mediated cytotoxicity. Chemotherapeutic agents such as mitomycin C, cisplatin, oxaliplatin and doxorubicin are used. Hyperthermic phase can vary from 60 to 90 min. Currently, HIPEC is being considered for peritoneal carcinomatosis, mesothelioma, desmoplastic small round-cell tumours, ovarian, colorectal and gastric malignancies. This procedure involves extensive abdominal/thoracic resection, which causes massive fluid shift, bleeding, coagulation abnormalities, electrolyte and metabolic derangements. Pre-anaesthetic assessment and workup should focus on the patient's ability to withstand these disturbances in physiology. Pulmonary function tests should be done for these patients to evaluate the pulmonary reserve.

Before initiation of HIPEC, the patient is made hypothermic up to 35 °C by using cold packs around the head, neck and axilla and by turning forced air warmers to ambient temperature. During the HIPEC phase, because of hyperthermic chemotherapy, the temperature increases and causes a hypermetabolic state, which is associated with hyperdynamic cardiovascular state with increased oxygen demand. As a consequence, metabolic acidosis is often seen which gradually clears in the postoperative phase. Patients should not be hypovolaemic before initiation and during the HIPEC phase to avoid nephrotoxicity due to platins. Cold intravenous fluids may be infused to prevent the core body temperature from rising above 39°C. Dextrose is used as a carrier solution for oxaliplatin, which is hypotonic and causes hyperglycaemia and hyponatraemia. Therefore, blood glucose and electrolytes need to be monitored frequently and corrected. The patient is often electively ventilated due to prolonged surgery.

14.2 Robotic Surgery

The role of robotic surgery is increasing due to improved surgical precision and the growing need for minimally invasive surgery. Robotic surgery is mainly used for pelvic malignancies and head and neck procedures. However, its scope is increasing and is currently being used for abdominal and thoracic surgery as well.

Important considerations for robotic surgery are mainly patient access and extreme positioning and its consequences. It is imperative to plan ahead for vascular access and extensions, and airway access and circuit extensions, as once the robot is docked there is not much scope to do any procedures. These are often prolonged surgical procedures and extreme positioning such as steep Trendelenburg or reverse Trendelenburg with a left or right tilt, is used for improved access for pelvic and abdominal procedures. Careful planning and attention should be given to padding of pressure points and haemodynamic disturbances due to position. This is compounded by the effect of pneumoperitoneum. Carbon dioxide insufflation can result in basal atelectasis and respiratory compromise, hypercapnia, reduced venous return, cardiac output and hypotension, and sympathetic stimulation. In Trendelenburg position, after prolonged surgery there is an increase in cerebral blood flow, intracranial pressure and venous congestion, resulting in swelling of the eyes and face and airway oedema; therefore, extubation strategy should be planned.

14.3 Proton Radiation Therapy

High-energy protons allow more accurate targeted delivery of energy to disease tissues thus sparing healthy tissues. These protons unlike conventional radiation deposit energy at the end of their path thus proton therapy has application in deep seated tumours such as those of the central nervous system. It is also used for treatment of paediatric retinoblastoma, prostate and bladder cancers and hepatocellular carcinoma. It consists of multiple treatment sessions (10–30), and the duration of each session may last up to 90 min. Due to longer treatment sessions, recovery of these patients may be delayed and therefore an adequately staffed recovery is essential. It also requires immobilisation devices like cradles and thermoplastic facemasks. Therefore, children and claustrophobic adults may require deep sedation for treatment sessions. Careful attention should be given to patient positioning during treatment as posterior fossa tumours may require prone positioning. Tight-fitting immobilisation facemasks may lead to airway compromise.

15 Acute Pain Management After Cancer Surgery

Poorly managed postoperative pain delays mobilisation, increases postoperative respiratory and thromboembolic complications and delays rehabilitation [43]. Effective pain relief helps with early mobilisation of patient, shortened hospital stay, reduced cost and improved patient satisfaction [44, 45].

An 11-point numerical pain assessment scale, where 0 is no pain and 10 is the worst possible pain imaginable, is used to quantify pain. The “Faces pain scale” is effective in those with language barrier and children above 4 years of age. The goal is to relieve pain with minimal side effects. The key to adequate pain control is to reassess the patient and determine if they are satisfied with the outcome.

Current evidence supports a multimodal approach to reduce opioid side effects (such as nausea and ileus) and improve pain scores. Multimodal analgesia uses a combination of analgesics or techniques each with a different mode of action; thereby lowering side effects by a reduction in analgesic doses, particularly of opioids. It usually consists of a combination of opioid and non-opioid analgesics with or without a regional block. Regional anaesthesia including wound infiltration, perineural injections, truncal/fascial plane blocks (e.g. transversus abdominis plane block, rectus sheath block), spinal and epidural analgesia are valuable components of multimodal approach [46, 47].

Epidural analgesia using local anaesthetics with or without an opioid provide superior analgesia than most other techniques and is used extensively in thoracic, abdominal and pelvic surgery. Epidurals are often used in high-risk surgeries with recent evidence showing improved pain control in the first 72 h compared to systemic opioids and positive effects on cardiac and pulmonary outcomes [48]. Of concern with epidural analgesia/anaesthesia is the insertion and removal of catheters in patients on oral or parental anticoagulants and antiplatelet agents because of an associated risk of neuraxial haematomas. The risk can be minimised by timing the same to the dose of the anticoagulant as briefly mentioned in Table 5.

Opioids such as morphine or fentanyl can be administered through the patient-controlled analgesia (PCA) device, special equipment that gives patient better control and autonomy over the amount of analgesic used. PCA is essentially a maintenance therapy; therefore, before initiating the PCA individually titrated doses should be administered, for optimum pain relief.

NSAID’s and paracetamol are useful in reducing opioid requirement and their side effects. Systematic reviews of randomised controlled trials (RCTs) have confirmed efficacy

Table 5 Guidance on timing of insertion and removal of epidural in patients on anticoagulant and antiplatelet medications[a]

	Minimum delay between last dose and placement or removal of epidural catheter	Minimum delay after placement or removal of epidural catheter and subsequent dosing
Heparin		
• No contraindication. • The risk of neuraxial bleeding may be increased in debilitated patients after prolonged therapy. • Patients receiving heparin for >4 days should have a platelet count assessed prior to neuraxial block and catheter removal (to rule out heparin-induced thrombocytopenia—HIT).		
IV Unfractionated heparin (UFH)	4–6 h	2 h
SC unfractionated heparin BD/TID dosage		
• Low dose (5000 U twice/thrice daily)	4–6 h	2 h
• High dose (<20,000 U/day)	12 h	Assess risk/benefit ratio
• Therapeutic dose (>20,000 U/day)	24 h	Assess risk/benefit ratio
Full anticoagulation of cardiac surgery	Currently, insufficient data and experience. Postoperative monitoring of neurologic function and selection of neuraxial solutions that minimise sensory and motor block is recommended to facilitate detection of new/progressive neurodeficit.	
Low-molecular-weight heparin (LMWH) **Dalteparin, enoxaparin, tinzaparin, etc.**		
Twice-daily dosing	24 h	4 h Avoid indwelling catheters during initiation of prophylactic or therapeutic BD dosing
Single-daily dosing	12 h	4 h Post op dose 12 h after epidural placement with catheter in situ
Traumatic needle or catheter placement may signify an increased risk of spinal haematoma, and it is recommended that this consideration be discussed with the surgeon. It does not necessitate postponement of surgery. However, initiation of LMWH therapy in this setting should be delayed for 24 h postoperatively.		
• Routine use of monitoring of the anti-factor Xa level is not recommended. • Antiplatelet or oral anticoagulant medications administered in combination with LMWH increase the risk of spinal haematoma. • Patients receiving LMWH for greater than 4 days should have a platelet count assessed prior to neuraxial block or catheter removal to rule out HIT.		
Warfarin		
• Stop warfarin at least 5 days prior to procedure. • Bridge with heparin infusion if continued anticoagulation is required. • Check INR on day of procedure and ensure <1.5 INR. • If INR >1.5. (a) Delay surgery (b) If surgery is urgent—consider alternative anesthetic/analgesic technique or reversal with 2.5–5 mg PO/IV vitamin K. (c) For emergency procedure consider reversal with fresh-frozen plasma/prothrombin complex concentrates. • Consider removal of neuraxial catheter prior to starting oral warfarin.		
Fibrinolytics/thrombolytics **(Alteplase, reteplase, tenecteplase, urokinase and streptokinase)**		
Absolute contraindication for neuraxial blockade • Thrombolytics drugs are contraindicated for 10 days following puncture of non-compressible vessels. • In patients who have received fibrinolytic and thrombolytic drugs, we recommend against performance of spinal or epidural anaesthetics. • Patients with epidural catheter who **unexpectedly receive fibrinolytic and thrombolytic therapy, fibrinogen level should be monitored to evaluate the presence of residual thrombolytic effect for appropriate timing of catheter removal.**		
Antiplatelet drugs		
Aspirin, –anti-inflammatory drug (NSAID's), cyclo-oxygenase inhibitors (COX2)	0 day in absence of other anticoagulant co-administration. Caution with performance of neuraxial techniques with concurrent use of other medications affecting clotting mechanisms, such as other (non-NSAID) antiplatelet agents, oral anticoagulants, UFH and LMWH.	
Antiplatelet drugs (P2Y12 receptor inhibitors)		
Clopidogrel	7 days	Daily maintenance dose take 6 h later Loading dose 24 h later
Ticlopidine (rarely used now)	10 days (10–14 days)	6 h
Prasugrel	7–10 days	6 h

(continued)

Table 5 (continued)

	Minimum delay between last dose and placement or removal of epidural catheter	Minimum delay after placement or removal of epidural catheter and subsequent dosing
Ticagrelor	5–7 days	6 h
Cangrelor	3 h	8 h
Antiplatelet drugs (GP IIb/IIIa antagonists) **AVOID due to platelet dysfunction**		
Abciximab	24–48 h	AVOID (if necessary, monitor neurological function)
Tirofiban	4–8 h	
Eptifibatide	4–8 h	
Other antiplatelet agents		
Dipyridamole	24 h	6 h
Cilostazol	2 days	6 h
Anti-Factor Xa—Fondaparinux		
Fondaparinux	36 h	12 h
Fondaparinux is recommended for thromboprophylaxis only with single needle pass, atraumatic needle placement and avoidance of indwelling neuraxial catheters. If this is not feasible, an alternate method of prophylaxis should be considered.		
Newer oral anticoagulants (factor Xa inhibitors)		
Rivaroxaban	Catheter placement after 72 h and removal after 22–26 h	6 h
Apixaban	Catheter placement after 72 h and removal after 26–30 h	6 h
Edoxaban	Catheter placement after 72 h and removal after 20–28 h	6 h
Betrixaban	Catheter placement and removal after 72 h Avoid neuraxial block if creatinine clearance (CrCl)l < 30 mL/min	5 h
Direct thrombin inhibitors		
Parenteral, e.g., desirudin, bivaluridin, argatroban	AVOID	–
Oral dabigatran	Catheter placement after 120 h CrCl > 80 mL/min–72 h CrCl—50–79 mL/min–96 h CrCl—30–50 mL/min—120 h CrCl < 30 mL/min—AVOID **Consider checking dilute thrombin time (dTT) or ecarin clotting time (ECT) if less than recommended duration**	6 h For patient with unanticipated administration with indwelling catheter **dabigatran dosing should be held for 34–36 h or the dTT or ECT should be assessed before removal.**
Herbal remedies (check for concomitant other blood thinners)		
Garlic	Stop 1 week prior, also stop other antiplatelet agents	
Dong quai/Danshen	Check INR with warfarin	
Ginkgo biloba	Check platelet function, discontinue 36 h before surgery	
Ginseng	Check coagulation profile, discontinue 24 h before surgery	

[a] Adapted from American Society Regional Anaesthesia guidelines [49]

of oral paracetamol for acute pain. Care should be taken not to exceed the 4000 mg per day limit due to risk of hepatotoxicity.

16 Adjuvants

“Adjuvant analgesics” are drugs with a primary indication other than pain, but are analgesic in some conditions. Central sensitisation through the descending pathway causes hyperexcitability in the spinal cord, which is thought to be responsible for chronic and neuropathic pain. Dampening of central sensitisation is important for prevention and treatment of both acute postoperative and chronic pain. These drugs are often used as part of multimodal analgesia, to achieve superior analgesia with lesser side effects. Various drugs used as adjuvants are listed below in Table 6.

Table 6 Adjuvant drugs for management of postoperative pain

Drug	Mechanism of action	Dose	Benefits	Concerns/cautions
Ketamine	Non-competitive NMDA receptor antagonist blunts central pain sensitisation at sub-anaesthetic doses.	Intraoperative IV bolus of 0.1–0.3 mg/kg alone or followed by postoperative infusion of 0.1–0.3 mg/kg/h for 24–72 h.	Its use is associated with reduction in the need/dose of other postoperative pain medications and pain scores [50]. May prevent development of persistent post-surgical pain however effective doses are yet to be established [51, 52].	May cause hallucinations and postoperative dissociative mental state. Contraindicated in patients with high-risk coronary or vascular disease, uncontrolled hypertension, intracranial or intraocular pressure, globe injuries, history of psychosis, sympatho-mimetic syndrome, hepatic dysfunction, recent liver transplantation and porphyria.
Lignocaine	It has analgesic, anti-inflammatory, and anti-hyperalgesic properties possibly mediated by inhibition of Na channels, NMDA and G-protein-coupled receptors.	IV Lignocaine, bolus of 1.5–2 mg/kg followed by an infusion of 2–3 mg/kg/h in the perioperative period and at a lower dose postoperatively.	Reduced opioid requirements and improved recovery of bowel function [50].	Lignocaine toxicity. Quality of evidence is limited due to inconsistency and quality of study [53].
Gabapentinoids Gabapentin	Decrease the dorsal horn sensitivity by inhibiting calcium-mediated neurotransmitter release through effects on α2δ-1 subunits. They also • Inhibit descending serotonergic facilitation • Stimulate descending inhibition • Have anti-inflammatory actions • Influence affective component of pain [54].	PO 600–1200 mg/day Max 1500 mg/day Administered 1–2 h prior to the surgery [50].	Associated with reduced opioid requirements and lower pain scores [50, 55].	Side effects such as dizziness, sedation, somnolence, with the higher doses. Dose should be adjusted in elderly and impaired renal function.
Pregabalin		150–300 mg/day administered 1–2 h prior to the surgery [50].		
Magnesium	Blockade of NMDA receptor and calcium channel.	IV bolus 50 mg/kg in 100 mL of normal saline given over 15 min during induction of anaesthesia followed by a continuous infusion at 15 mg/kg/h during surgery was found to significantly reduce postoperative pain.	Perioperative infusion has shown to reduce opioid consumption and pain scores in the first 24 h with no serious side effects [56].	Bradycardia, hypotension,muscle weakness and potentiation of non depolarising muscle relaxants, ECG changes such as prolongation of PR & QT intervals. Should be used with caution and avoided in those with pre existing AV blocks and chronic neuromuscular diseases such as myasthenia graves.

NMDA N-methyl-D-aspartate, *PO* per-oral, *IV* intravenous

17 Anaesthesia and Cancer Recurrence

Advances in surgery, chemotherapy, and radiotherapy have improved outcomes after surgery for cancer. However, cancer cells that may be released into the circulation during surgery may lead to cancer recurrence and metastases. Anaesthetic drugs and techniques may significantly contribute to this process and thereby present an opportunity for intervention.

Surgery, perioperative stress, anaesthetics and analgesics may modulate the immune-surveillance mechanisms and overwhelm host defences that normally maintain a balance between immunity and carcinogenesis. This may lead to escape of cancer cells and tilt the scales towards a more pro-tumorigenic micro-environment. Choice of anaesthetic technique and drugs used in the perioperative period has been an area of interest in the last few years, as they may affect postoperative immune function and inflammation which may have a role in cancer progression and metastasis. Volatile anaesthetic agents, in particular, have been shown to exhibit profound immunosuppressive effects and may be associated with adverse long-term outcomes compared to total intravenous anaesthesia (TIVA). In comparison, propofol has a favorable profile and inhibits cancer cell activity. Opioids suppress natural killer (NK) cell function as well as have inhibitory effect on T and B lymphocyte functions by direct and indirect mechanisms [57], thus promoting tumour recurrence and metastases.

Ketamine in low dose suppresses NK-cell cytotoxicity and inhibits the production of pro-inflammatory cytokines [3, 58, 59]. Endogenous and exogenous opiods have differing effects on the immune balance. Endorphin increases NK-cells cytotoxicity and favours anti-inflammatory cytokines and has anti-cancer effects. Exogenous opioids on the other hand suppress the immune function by inhibiting humoral and cell-mediated immunity (CMI) and promote cancer cell proliferation and angiogenesis [58]. Propofol inhibits tumour size, angiogenesis of cancer and does not suppress CMI thus has an anti-cancer effect [58, 59]. Local anaesthetics attenuate afferent neural transmission by sympathetic blockade and thus prevent pain and reduce neuroendocrine stress response and thus preserving CMI. They may directly stimulate natural NK-cell activity. Local anaesthetics block voltage-gated sodium channels and thereby prevent activation of prometastatic pathways. In addition, use of regional anaesthesia reduces the dose of exogenous opioids and volatile anaesthetics suggesting a favourable effect on the perioperative immune balance [58, 60].

Despite animal studies, there is very little human data to conclude that a particular anaesthetic is associated with worse clinical outcomes [61, 62]. A randomised trial found that regional anaesthesia-analgesia with paravertebral block and propofol sedation for surgery did not reduce breast cancer recurrence compared to general anaesthesia with volatile anaesthesia (sevoflurane) and opioids [63]. These data suggest that genral anaesthesia with opioids and volatile agents can safely be used for cancer surgery. However, regional anaesthesia and intravenous anaesthesia with propofol should be used where appropriate for clinical indications.

18 Conclusion

Elderly patients with sedentary lifestyle and multiple comorbidities along with cancer therapy adversely affect overall physical fitness and nutrition which in turn are associated with poor postoperative outcomes. Perioperative care plans should take this into consideration and should be individualised to improve physical fitness, optimise medical conditions and anaemia, implementation of evidence-based and outcome driven perioperative care pathways to promote early recovery and reduced morbidity. Preclinical studies suggest that anaesthetic-induced immunosuppression may affect tumour biology and promote cancer recurrence in patients with certain types of cancer. Causal link between anaesthetic techniques on residual disease, immune function, survival is yet to be elucidated. Future research in this area will provide more definitive answers.

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Transfusion Medicine in Oncology

Priti Desai, Anisha Navkudkar, and Sunil Rajadhyaksha

1 Introduction

Blood transfusion therapy is complex and multifaceted. Though the general principle of transfusion therapy is same to all patients, special considerations are required for oncology patients. Transfusion support is required for oncology patients during their course of treatment as they undergo chemotherapy, radiotherapy, and surgical intervention [1]. Oncologic conditions may induce myelosuppression resulting in anemia, thrombocytopenia, and granulocytopenia during the treatment course. Hence, these patients require all kinds of blood transfusion support. It is therefore critical that blood transfusion services should be able to provide the necessary hemotherapy support in consultation with the oncologists. Although the introduction of recombinant hematopoietic growth factors and peripheral stem cell transplant has decreased the need of blood products, it has not eliminated the need of blood component therapy. Transfusion of blood components is associated with adverse events hence probable benefits of transfusion must be assessed against risks associated. Evidence-based medicine (EBM) enhances clinical decision making by incorporating best research evidence with clinical proficiency and patient parameters [2].

2 History of Transfusion Medicine in India

The first blood bank in India was established in Kolkata at the All-India Institute of Hygiene and Public Health in 1942 and was shifted to Kolkata Medical College, as the first civilian blood bank in the country in 1945 [3]. In earlier times, till 1970 collected blood was stored in bulky and fragile glass bottles which had to be washed and sterilized for reuse. With the glass bottles, separation into different blood components was complicated, lacked consistency, and prone to bacterial contamination. Subsequently, plastic bags made separation of blood much easier, allowing focussed management of conditions such as anemia and bleeding especially in treatment of patients with leukemia and lymphoma who underwent aggressive chemotherapy and bone marrow transplantation. With the establishment of disposable plastic blood bags, blood components could be stored and transported more easily. Blood transfusion services have transcended from initial process of withdrawal of blood, storage, and transfusion to complex laboratory technologies, patient care and evidence-based management. The blood center-based services include serological aspects of blood, advanced immunohematology techniques, preparation of blood components, modification of blood components, multicomponent therapy, testing for transfusion transmissible infections (TTIs), nucleic acid amplification testing (NAT), and research of several aspects of blood safety. Apheresis technology, cellular therapies, and novel immunotherapies are included in patient care services. Blood donor motivation, recruitment, retention, rare donor registries, and apheresis donors are crucial challenging tasks in blood transfusion services. Evidence-based medicine is forming the basis of clinical transfusion practices these days. Also, hemovigilance and transfusion audits are important for optimum patient services. The comprehensive, centralized, and a well-organized Hemovigilance program of India generates evidence-based suggestions for transfusion safety and precautionary measures [4, 5].

3 History of Transfusion Medicine in Oncology

Transfusion support is an important supportive therapy for patients with hemato-oncologic disorders. Due to the myelosuppression and immunosuppression, they require multiple blood transfusions and at risk for transfusion related adverse events. Hemato-oncologic patients are at increased risk for

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alloimmunization, certain transfusion transmitted infections (TTIs), transfusion-associated graft vs. host disease (TAGVHD), and transfusion-related immunomodulation (TRIM) as compared to the general patient population. Also, transplant patients might pose unique challenges to blood transfusion services due to potential ABO incompatibility in some cases. Therefore, appropriate therapy to these patients is provided by careful selection and modification of blood components as per the requirements. The transfusion safety in oncology patients is improved by significant advances in transfusion therapy including advanced immunohematology techniques for antibody identification and providing appropriate blood components.

4 Physiological Aspects of Blood

4.1 Red Cell Kinetics

The primary function of red blood cell is to transport oxygen from lungs to other tissues of the body. Oxygen delivery is regulated by number of circulating erythrocytes in the blood, which depends on rate of aging erythrocyte removal and rate of reticulocyte entry. Normal bone marrow produces almost precisely the same quantity of erythrocytes daily as lost through senescence. When increased amount of erythrocytes are lost in bleeding or hemolysis, new erythrocyte production rapidly increases to maintain constant erythrocyte number. The regulated production of erythrocyte is controlled by negative feedback mechanism, which involves oxygen supply and consumption, the hormone erythropoietin (EPO) produced in the kidneys, and the erythroid progenitor cells in the bone marrow dependant on EPO. It also depends on sufficient supplies of specific nutrients like iron, folate, and vitamin B_{12}. Disorders of hematopoietic system like malignancy inhibit the erythropoietic process.

4.2 WBC Kinetics

WBCs especially neutrophils are the body's main defence cells against bacterial organisms. Increased neutrophil counts are typical of infections, chronic myeloid leukemia and other myeloproliferative disorders (MPD) and reduced neutrophils can indicate aplastic anemia, myelodysplastic syndrome (MDS), acute leukemia, and other disorders affecting bone marrow function. Production and differentiation of neutrophils and other granulocytes are labeled as myelopoiesis or granulopoiesis. It is controlled by hematopoietins and cytokines which stimulate colony formation from progenitor cells in the bone marrow. Granulocyte colony-stimulating factor (G-CSF) is the primary cytokine-regulating granulopoiesis, as it stimulates granulopoiesis at various stages of granulocytic differentiation. GCSF significantly expands the marrow neutrophil mitotic pool and reduces the transit time of the post mitotic pool. Mean marrow neutrophil transit time of a postmitotic pool in healthy person is 6.4 days, whereas with G-CSF it is 2.9 days [6].

4.3 Platelet Kinetics

Platelet production or megakaryocytopoiesis starts with hematopoietic stem cells (HSCs) commitment toward megakaryocyte lineage and involves proliferation, maturation, and differentiation of megakaryocytic progenitors. The primary growth factor for the expansion of megakaryocyte (MK) lineage is thrombopoietin (TPO), which induces concentration determined proliferation and maturation of megakaryocyte. The key transcription factors involved in common myeloid precursor (CMP) are PU.1, which regulates granulocyte-monocyte progenitors, and GATA-1, which leads to differentiation of megakaryotic-erythroid precursors (MEPs) [7]. The normal platelet production kinetics is indirectly measured by establishing the turnover rate of circulating platelets. The lifespan of platelets is 9.5 ± 0.6 days and platelet loss is usually linear. Reticulated platelets are the platelets, which are newly released from megakaryocyte into circulation. They are characterized by increased RNA content and reflects on thrombopoietic activity of bone marrow [8]. An increase in reticulated platelets is observed whenever there is peripheral destruction of platelets and decrease in number is seen in case of hypoproliferative disease of marrow such as marrow aplasia due to chemotherapy, radiation, or aplastic anemia.

4.4 Normal Hemostasis

Hemostasis is the physiologic process that halts bleeding after injury to the vessel and depends on cellular components and plasma proteins. Arteriolar vasoconstriction is followed by adhesion and aggregation at blood vessel injury sites (primary hemostasis). The extrinsic pathway of blood coagulation is commenced when blood is exposed to tissue factor (Secondary hemostasis). Permanent plug formation includes fibrin deposition, which restricted by mechanisms of the natural anticoagulant system. Ultimately, fibrin is consumed by the fibrinolytic system, the key components of which are plasminogen and tissue-type plasminogen activator (tPA).

5 Blood Group Antigens and Antibodies

Most blood group antigens are glycoproteins, and their specificity is mostly defined by the oligosaccharide chain (e.g., ABO) or protein sequence (e.g., MN, Kell, Duffy, Kidd, etc.). Each blood group system denotes either a single gene or a compilation of closely linked homologous genes. The 36 human blood group system genes have been determined, sequenced, and polymorphisms are known. Blood group antigens are conventionally tested by hemagglutination methods, the tube technique being the gold standard for many years. High throughput and various antigen/antibody testing methods are available. Limitations of serology techniques in recently transfused patients where both donor and patient red cells co-exist or unavailability of some typing reagents have cemented the way for molecular blood grouping.

6 Blood and Blood Components

6.1 Whole Blood

A blood donor donates whole blood which can be processed into different. Whole blood contains 350 mL/450 mL ± 10% of donor's blood with anticoagulant solution. Hematocrit of whole blood is 30–40%. Stored whole blood has nonfunctional platelets and absence of labile coagulation factors. The ability to prepare blood components is advantageous as it allows optimal survival of each constituent and allows specific blood component to be transfused according to the patient requirement. Constant supply of blood components adds to the blood inventory.

6.2 Packed Red Blood Cell (pRBC)

Packed red blood cells (pRBC) are prepared by removing maximum plasma from a unit of whole blood. Red cells settle in the lower portion of bag due to the sedimentation or centrifugation owing to higher specific gravity while the plasma is transferred into a satellite bag. Red cells with additive (Adsol or SAG-M) have hematocrit of 50–60%, minimum plasma and buffy coat (leukocytes and platelets).

6.3 Platelet Concentrates

Platelet concentrate prepared from whole blood is called random donor platelets (RDP) and is stored with agitation at room temperature (20–24 °C) within 6–8 h of collection. It is prepared using any of the following two methods:

(a) By using CPD-A1/CPD-ADSOL or SAG-M triple or quadruple blood bags and refrigerated centrifuge, also known as the platelet-rich plasma (PRP) method.
(b) By buffy coat removal method using blood collection bags (top and bottom) and automated component extractors.

6.4 Fresh Frozen Plasma (FFP)

FFP is plasma prepared from a single donor either by whole blood donation or by plasmapheresis and rapidly frozen within 6–8 h of collection. It contains all coagulation factors and care must ensure to preserve their activity during collection of blood, freezing, and thawing. One unit of factor activity is the amount present in 1 mL of fresh, average normal plasma with one tenth part citrate anticoagulant.

6.5 Cryoprecipitate

Cryoprecipitate is the insoluble portion of plasma remaining after thawing the fresh frozen under controlled conditions. Cryoprecipitate is reconstituted before issue by placing in an overwrap in a 37 °C water bath until the cryoprecipitate has dissolved. Cryoprecipitate should be resuspended thoroughly by gentle massaging. Once thawed, cryoprecipitate should be transfused within 4 h and should not be refrozen.

6.6 Granulocyte Concentrate

Granulocytes for transfusion can be from buffy coat prepared during whole blood separation into components or granulocytes collected by apheresis technology. Granulocytes are transfused to patients with severe neutropenia unresponsive to antibiotics.

6.7 Components Collected by Apheresis Technology

1. **Single Donor Platelets (SDP):**

   Platelets obtained from a single donor by plateletpheresis procedure (removal of platelets from a donor with return of remaining blood components, i.e. red cells, white cells, and plasma) is called single donor platelets (SDP). One SDP is equivalent to platelets obtained from five to six whole blood donations. Patients transfused with SDP are exposed to a smaller number of donors thus preventing the chances of refractoriness to a great extent.

2. **Granulocytes concentrate:**

   Apheresis allows selective collection of a comparatively higher dose of granulocytes than would be found in whole blood with the added advantage for the donor of marginal red cell loss. Minimum yield of granulocyte collected by apheresis must be 1×10^{10} granulocytes/unit.
3. **Source plasma:**

   Source plasma is plasma collected from healthy, voluntary donors by a process called plasmapheresis and is used for further manufacturing into plasma-derived products (fractionation).

7 Modifications of Blood Components

7.1 Leukoreduction

Different methods applied for leukocyte removal are red cell washing, buffy coat removal, use of leukocyte filters, freezing, and deglycerolization of red cells and blood component collection by the apheresis technique. Among all these methods, use of third-generation leukocyte filters and apheresis techniques are most efficient to achieve quality standards. Leukoreduction helps in reduction in febrile nonhemolytic transfusion reaction (FNHTR), HLA alloimmunization and platelet refractoriness, CMV transmission risk, TRALI, TRIM, etc.

7.2 Irradiation

Irradiated blood components prevents transfusion associated graft versus host disease (TA-GvHD), which is a rare but commonly fatal complication of transfusion of cellular blood components. The mechanism is engraftment, proliferation, and mediation of a cellular immune response by the donor T-cells against host tissues, resulting in harm to skin, liver, gastrointestinal tract, and bone marrow [9]. TA-GVHD usually occurs in immunocompromised patients but can also occur in immunocompetent recipients or patients who may have only a mild immunodeficiency due to transfusion of allogeneic immunocompetent T-lymphocytes.

7.3 Washing

Washing of red cells or platelets eliminates 70–95% of leukocytes with an associated loss of 15–20 mL of red cells. It helps in removal of plasma proteins and microaggregates [10]. Washing is indicated in patients with frequent episodes of FNHTRs and allergic urticarial reactions, patients having developed antibodies to plasma proteins, IgA-deficient patients who has anti-IgA, patients with paroxysmal noctural hemglobiuria (PNH) sensitive to complement.

7.4 Pathogen Reduction

Pathogen reduction technology (PRT) has been established to improve blood safety. The principle of current pathogen reduction strategies is based on modifying DNA or RNA templates and making them unavailable to DNA or RNA polymerase. Various platforms of pathogen reduction include treatment with psoralens, alkylating compounds, riboflavin, methylene blue, and solvent–detergent (SD). Pathogen reduction systems have been devised for RBC, plasma, and platelets and is found to be effective for a variety of pathogens including lipid-enveloped and nonenveloped viruses, bacteria, and parasites [11]. The methods used should remove or inactivate pathogens, including emerging ones, with maintaining the function and shelf life of the blood components. In addition, any chemicals used, and the resulting product must be demonstrated as nontoxic and nonimmunogenic.

8 Special Considerations in Oncology Patients

8.1 Pretransfusion Testing Issues in Oncology Patients

- **Issues related to blood grouping:**

  Oncology patients can pose problem during blood grouping due to underlying disease condition, immunosuppression, chemotherapy, ABO incompatible transplant, etc. Table 1 discusses about the different types of discrepancies and methods to resolve it.
- **Alloimmunization in Oncology patients:**

  Red cell alloimmunization is a late complication of blood transfusions affecting 8–12% of all recipients [13]. The alloimmunization percentage increases considerably if patients are multiply transfused like with thalassemia, sickle cell anemia, leukemia, myelodysplastic syndrome, etc. But there is low incidence of alloimmunization of oncology patients due to the immunosuppressive character of chemotherapy and radiation therapy.
- **Antibody screening and identification in oncology:**

  In patients with antibody screen positive, antibody identification by cell panel should be performed. The pattern of antigen expression should be diverse so that it will be feasible to distinguish different antibodies and should include homozygous expression of Rh, Duffy, Kidd, and MNSs antigens. Phenotype matched compatible blood should be provided in antibody positive cases.
- **Antibody titer:**

  Once an antibody is identified, it is occasionally useful to know the antibody titer that is present and antibody titration can help determine antibody concentration levels. Twofold serial dilutions of serum containing the anti-

Table 1 Types of grouping discrepancies [12]

Type of grouping discrepancy	Causes	Resolution
Type 1 (Missing antibody)	• Patients with a leukemia or lymphoma • Patients using immunosuppressive drugs with hypogammaglobulinemia • Patients with bone marrow or stem cell transplantations (patients develop hypogammaglobulinemia and start producing a different RBC population from that of the transplanted stem cells)	• Obtaining proper history • Enhance weak reaction in the serum • Increasing serum:cell ratio • Lower temperature of testing/incubation at 4 °C for longer time
Type 2 (Missing antigen)	• Subgroups of A (or B) may be present • Leukemias may lead to weakening of A or B antigens • Hodgkin's disease • The "acquired B" phenomenon is most often associated with diseases of the digestive tract (e.g., colon carcinoma) • Chimerism – Blood transfusions (e.g., group O red cells given to an A or B patient) – Transplanted bone marrows or peripheral blood stem cells of a different ABO blood group	• Increase cell:serum ratio • Increase incubation time at room temperature for >30 min • Incubate at 4 °C for longer time (15–30 min)
Type 3 (Rouleaux formation)	• Elevated levels of globulin due to certain disease conditions such as multiple myeloma, Waldenström's macroglobulinemia, other plasma cell dyscrasias, and certain moderately advanced cases of Hodgkin's lymphomas • Elevated levels of fibrinogen • Plasma expanders such as dextran and gelofusin used in cases of massive transfusions	• Washing patient's RBCs multiple times with saline • Performing saline replacement technique. (removed serum is replaced with equal volumes of saline. In true agglutination, RBC clumping will persists after the addition of saline)
Type 4 (Miscellaneous)	• Cold reactive autoantibodies in which RBCs are heavily coated with antibody which led to spontaneous agglutination, independent of the specificity of the reagent antibody • Patient has circulating RBCs of more than one ABO group due to RBC transfusion or marrow/stem cell transplant • Irregular/unexpected auto/allo antibodies	• The patient's RBCs can be incubated at 37 °C for a brief period, then washed three times with saline at 37 °C and retyped • The patient's RBCs can be treated with 0.01 M dithiothreitol (DTT) to disperse IgM-related agglutination • As for the serum, the reagent RBCs and serum can be warmed to 37 °C, mixed, tested, and read at 37 °C and can be converted to the antihuman globulin phase if necessary

body are tested against RBCs suspension that possesses the target antigen. Antibody titer plays an important role in selection of blood products in HSCT patients.

- **AIHA in Oncology:**

  In the case of AIHA, autoantibodies directed against the patient's own red blood cells cause hastened red cell destruction. AIHA can be seen in malignancies like leukemia, lymphoma, ovarian tumors, B-cell neoplasms, etc. These patients majorly have warm antibodies reacting at AHG phase. In case of presence of autoantibodies and alloantibodies, adsorption techniques should be used. autoadsorption, homologous adsorption, and differential adsorption are various techniques of adsorption.

- **Chimerism:**

  The presence of two cell populations in an individual is termed as chimerism. It is observed in transplanted bone marrows or peripheral blood stem cells of a different ABO blood group [14]. Chimerism results are typically mixed field. Persistent chimerism after blood transfusion may lead to development of TAGVHD in the recipient.

9 Transfusion in Oncology Patients

- **Packed red cells:**

  The objective of red cell transfusion is same as that for general patients—to increase oxygen carrying capacity of blood. There are no evidence-based guidelines that suggest transfusion trigger in oncology patients. Therefore, oncology patients must be transfused for symptomatic anemia or at predetermined hemoglobin levels as decided by hospital's transfusion policy. For most oncology patients, no special consideration is required for appropriate selection of ABO group for RBC units. However, the choice of appropriate ABO group becomes difficult in ABO mismatch allogenic hematopoietic stem cell transplant (HSCT). For major ABO-incompatible stem cell recipients, recipient type RBCs are provided until there are no detectable incompatible antibodies and the direct antiglobulin test (DAT) is negative. Any plasma containing component (FFP and platelets) should be donor type, to prevent passive transfer of incompatible A and B antibodies.

For minor ABO-incompatible marrow transplants, RBCs should be donors' type, and plasma components should be recipient type until recipient RBCs are no longer detected. For transplants that are bidirectional (both major and minor ABO-incompatible), RBCs should be group O and plasma components should be of group AB.

- **Platelets:**

  Platelet transfusion is a first-line therapy for acute bleeding in patients with thrombocytopenia or those receiving antiplatelet medication. In earlier times, 1990s, the target for routine bleeding prophylaxis was to keep platelet counts greater than 20,000/μL. However, recent trials have demonstrated that spontaneous hemorrhage is unlikely; even with platelet counts as low as 5000–10,000/μL. In addition, patients transfused under more stringent guidelines have shown no change in morbidity and significantly use fewer blood components, thereby reducing the risks of chronic transfusion exposure and thus platelet refractoriness. Although ABO matched platelet transfusions are preferred, ABO mismatched platelets can be given. However, the use of ABO-mismatched platelets in oncology patients can result in reduced therapeutic benefit due to platelet refractoriness.

- **Fresh frozen plasma:**

  The indications for transfusion of plasma and plasma-derived components, such as cryoprecipitated antihemophilic factor (AHF), are similar in oncology and general patient populations. No special consideration is offered to the selection of ABO group for plasma or cryoprecipitate if the unit is ABO identical/compatible with the recipient. Donor and recipient Rh types are not a considered for plasma or cryoprecipitate transfusion. For patients who have undergone allogeneic HSCT, the selection of ABO group plasma should be based upon consideration of major and minor mismatches as mentioned earlier.

- **Granulocytes concentrates:**

  Granulocyte transfusions are required in oncology patients with severe neutropenia to treat life-threatening infections with antibiotic resistance [15]. The decision to initiate granulocyte transfusion usually arises in patients with severe neutropenia or failure to respond to antibiotics with a reasonable chance at sustainable marrow recovery after resolution of the underlying infection.

10 Transfusion Reactions

Any transfusion-related adverse event that occurs during or after the transfusion of whole blood, blood components, or human-derived plasma components is defined as transfusion reaction. They are also classified according to the time interval between transfusion and the presentation of adverse effects (Fig. 1).

An **acute transfusion reaction is** one with signs or symptoms presenting during or within 24 h of transfusion while the one presenting after 24 h of transfusion is defined as a **delayed transfusion reaction**. Transfusion reactions once recognized should be immediately stopped and reported to the Department of Transfusion Medicine. Management of transfusion reactions is discussed in Table 2.

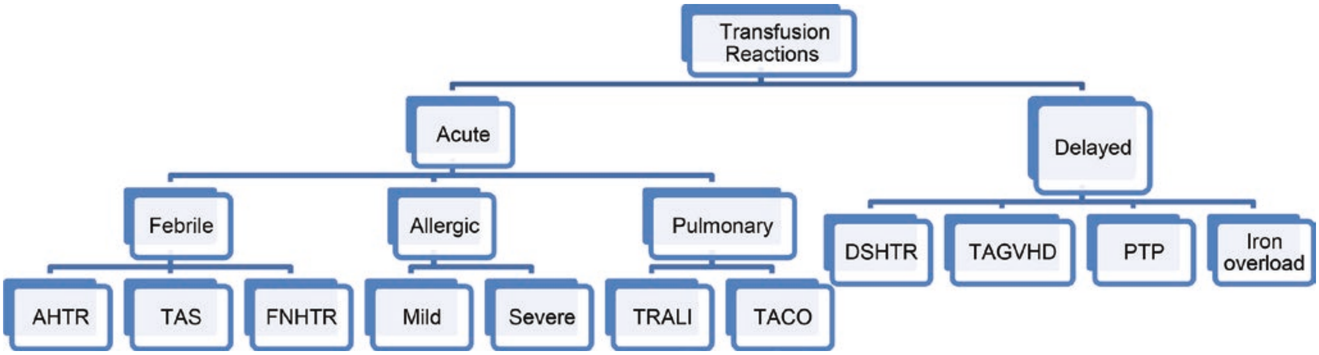

Fig. 1 Classification of transfusion reactions

Table 2 Management of transfusion reactions

Sr. No	Reaction	Treatment
1	Acute Immune Hemolytic Transfusion Reaction (AHTR)	Stop the transfusion, maintain vascular access, maintain blood pressure, renal blood flow, and treat DIC if present
2	Acute non-immune hemolytic transfusion reaction (ANIHTR)	Stop the transfusion, maintain vascular access, Maintain renal blood flow
3	Transfusion-associated sepsis (TAS)	Stop the transfusion, maintain vascular access, Consider initial broad-spectrum antibiotic treatment
4	Febrile nonhemolytic transfusion reaction (FNHTR)	Treat with antipyretics, for rigors treat with meperidine
5	Allergic, Mild	Temporarily stop the transfusion, treat with antihistamines and if symptoms improve restart transfusion
6	Allergic, Severe	Stop the transfusion, maintain vascular access, treat with subcutaneous epinephrine, maintain blood pressure, provide respiratory support
7	Transfusion-related acute lung injury (TRALI)	Stop the transfusion, maintain vascular access, supplemental oxygen, mechanical ventilation
8	Transfusion-associated cardiac overload (TACO)	Upright posture, supplemental oxygen, diuresis
9	Delayed serologic hemolytic transfusion reaction (DSHTR)	As needed transfuse antigen negative, AHG cross-matched compatible PRBC
10	Delayed hemolytic transfusion reaction (DHTR)	As needed transfuse antigen negative, AHG cross-matched compatible red cells
11	TA-GVHD	Supportive treatment with Immunosuppressive agents and Immunomodulators
12	Post transfusion purpura (PTP)	Intravenous immunoglobulin
13	Iron overload	Use of iron-chelating agents

11 Conclusion

Transfusion support is a crucial therapy for patients with hemato-oncology disorders. However, their immunosuppressed state and repeated exposure to transfusion; they are often at more risk for transfusion reactions. Compared to general patient populations, oncology patients are at increased risk for certain transfusion-transmitted diseases, red cell and platelet alloimmunization, TA-GVHD, and immunomodulation. In addition, HSCT patients present distinct challenges for transfusion support as they require particular evaluation for potential ABO incompatibility. Proper selection of blood components and modification if required is therefore necessary to provide appropriate transfusion support to these patients. Considerable advances have been made in transfusion services, including sensitive donor testing and alternatives to blood component therapy, which will continue to improve transfusion safety for oncology patients.

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Palliative Care in Oncology

Naveen Salins and Mary Ann Muckaden

Abbreviations

ASCO	American Society for Clinical Oncology
BDI	Beck Depression Inventory
CQC	Care Quality Commission
DT/PCL	Distress Thermometer and Problem Check List
ELICIT	End of Life Care in India Taskforce
ESAS	Edmonton Symptom Assessment Scale
FATE	Family Assessment of Treatment of End of Life
HADS	Hospital Anxiety and Depression Scale
HDRS	Hamilton Depression Rating Scale
IAPC	Indian Association of Palliative Care
ICMR	Indian Council of Medical Research
ISCCM	Indian Society of Critical Care Medicine
MDAS	Memorial Delirium Assessment Scale
NABH	National Accreditation Board of Hospital
NDS	Nurse Delirium Scale
NSAIDs	Non-steroidal Anti-inflammatory Drugs
POS	Palliative Outcome Scale
QOD	Quality of Death Hospice Scale
QODD	Quality of Death and Dying
QUEST	Quality of End-of-Life Care and Satisfaction with Treatment
SEER	Surveillance Epidemiology and End Results

1 History of Palliative Care in India

In 1986, Dr. Luzito D'Souza, a surgical oncologist, established the first hospice called Shanti Avedana in Mumbai, which was supported by dedicated nuns from the Sisters of The Holy Cross. In late 1980s, the initial cancer palliative care services were provided through Tata Memorial Centre. Then, patients with cancer having severe pain were prescribed a tablet called A and O (aspirin and opium). It was manufactured by Haffkine Institute, Mumbai [1]. In 1993, The Pain and Palliative Care Society (PPCS) at Calicut Kerala started home-based palliative care services. It evolved into neighbourhood network in palliative care (NNPC) program a community-led service capable of providing home-based palliative care to all those in need. This program facilitated enormous social mobilization, something that was possible in the socially conscious State of Kerala [2]. In rural areas, the community owned units were set up with the help of the PPCS. The Indian Cancer Society a public charitable trust along with Rotary Bangalore Indiranagar was instrumental in setting up a modern hospice in Bangalore called *Karunashraya* in 1994. In 2010, the palliative care was recognised as a medical subspecialty by the Medical Council of India (MCI). The Certificate Course in Essentials of Palliative Care was started by the Indian Association of Palliative Care in 2007 and The National Fellowship in Palliative Medicine (NFPM) a post-graduate training program in palliative medicine for medical professionals in India started in 2004. In 2012, the Tata Memorial Hospital Mumbai started the first specialist Palliative Medicine training [3]. The *Indian Journal of Palliative Care* (IJPC) a peer-reviewed journal, published four times a year by the Indian Association of Palliative Care. It came into existence in 1995, and it is online since 2007.

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2 Palliative Care Need in India

In India, palliative care need is estimated as 175–275 per 100,000 population. India is classified under high palliative care requirement region of the world. Around 70–140 per 100,000 population in India with cancer require palliative care and the rest needing palliative care have progressive non-malignant conditions and HIV/AIDS [4].

More than one million new cancer cases are diagnosed each year in India and with over 80% present with stage III and stage IV diagnosis [5]. More than two-thirds of them are often incurable at the time of presentation and are only candidates for palliative care [6]. Besides these significant numbers of patients who receive treatment for cancer recur, and it is often not amenable to effective cancer directed treatment. About 80% patients with advanced cancer experience moderate to severe pain due to inequitable access to essential pain relief medicines [7]. Hence, palliative care intervention and attention to pain management are warranted early in the course of cancer treatment [8].

A population-based study conducted in a large city of India showed that most people preferred to die at home [9]. In an Indian setting, home-based palliative care might be a cost effective, relevant and practical option [10]. Patients often receive high-cost inappropriate medical interventions at end of life, due to lack of palliative care provision. It often drains the resources of patients and family [11]. Significant numbers of discharges against medical advice (DAMA) from the Indian ICUs are often due to high cost and unavailability of appropriate care at end of life [12]. Unilateral DAMAs preclude patients from receiving care at end of life. The current health spending in India is 4% of the GDP, and there are limited allocated budgetary provisions for palliative care. A significant proportion of the Indian population spend out of pocket for their health-related expenses leading to millions of families are becoming poorer every year due to rising health-related expenditures and most of these expenses are related to treatment during end of life. A universal access to palliative care might avoid this [13].

3 Principles of Palliative Care

Palliative care aims to better the quality of life of patients and their families met with the problems associated with an illness that might limit or alter the course of their lives. It is the goal is to prevent and relieve suffering through prompt recognition, assessment and treatment of physical symptoms, psychosocial issues and spiritual distress.

Palliative care

- Provides symptom management and relief of distress
- Facilitates natural death and acknowledges that dying as a normal process
- Intends neither to accelerate or defer death
- Embeds the emotional and spiritual aspects of care
- Enables assistance to patients to live as actively as possible
- Facilitates reinforcement to the caregivers during the illness and bereavement
- Approach to care is through a multidisciplinary team
- Betters quality of life and positively impacts the illness journey
- Is appropriate to be initiated during initial stages of illness alongside treatment directed at disease management

According to the American Society for Clinical Oncology (ASCO), the palliative care should be integrated with standard cancer care early in the course of treatment for patients with locally advanced disease, metastatic spread or with a high symptom burden.

- Palliative care referral should be made within 8 weeks of diagnosis of metastatic illness
- Palliative care services should be integrated early in both ambulatory and inpatient setting concurrently with active treatment [5, 14].

4 Symptom Management

It is important not only to assess common symptoms but also their severity. The most commonly used scale is the Edmonton Symptom Assessment Scale (ESAS) [15]. Symptom management in palliative care require accurate and meticulous assessment, assessing and addressing non-physical as well as physical issues, using different approaches to manage difficult to control symptoms, weighing risk versus benefit assessments when side effects of therapy occur, communication to the patients and their families, using a multidisciplinary approach and continued reassessment.

The principles of EEMAA facilitates excellent symptom control, which is a critical component of effective palliative care and is based on the

- Evaluation—diagnosis of each symptom before treatment
- Explanation—to the patient before treatment

- Management—individualised treatment
- Monitoring—continuing review of the impact of treatment
- Attention to detail—no unwarranted assumptions

Adhering to such a systematic approach, helps not only in better symptom control but also increases compliance and holistic care.

Generally, pain in patients with cancer, especially in a palliative care setting, is described as a multi-faceted experience where sensory, affective, cognitive and behaviour are its four key facets. Often these patients suffer moderate to severe pain [16]. It is often present at multiple sites exhibiting diversity in intensity and has a complex underlying pathophysiology and clinical presentation [17]. The sensory component of pain manifests its affective dimension in the form anxiety, low mood and distress [17]. The person experiencing the pain cognises it as unpleasant experience, adverse emotions and might influence the entire personhood of the individual [18]. They could present with certain behavioural manifestations like abnormal posture, curtailment of activities of daily living, isolation from society, avoiding treatment and not complying with the prescription and impacting the pain relief and holistic care of the patient [19]. There is a significant difference in cancer pain management in an outpatient setting, home setting, hospital setting and hospice setting. These differences are further discussed below.

4.1 Guidelines for Cancer Pain Management in Ambulatory Palliative Care Setting

In an outpatient palliative care setting, the algorithm often used is the analgesic step ladder provided by the World Health Organization (WHO). It is founded on the intensity of pain (mild, moderate or severe) described by the patients and recorded using a numerical rating scale. Mild pain is often treated using non-opioid preparations like non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol (acetaminophen). Moderate pain is managed using weak opioids like Codeine, Tramadol and Tapentadol either singularly or along with non-opioids and adjuvant analgesic. Severe pain needs strong opioids like Morphine, Fentanyl and Methadone used by itself or along-side a non-opioid or adjuvant analgesic [20, 21]. The analgesic ladder by WHO provides easy applicable sequential steps for specialists and generalists pain management. In a chronic pain setting, it might avoid misuse of opioids and might lessen the apprehension of addiction and legal action. It can be applied across the world in any setting and might be of great value in the developing countries where there is paucity of pain specialists. Research has shown that stepladder approach enabled excellent pain control for a significant duration in vast majority of patients [22]. Up to 76% of them might achieve excellent pain control with this algorithm; and 12% of them got satisfactory betterment and 12% had no benefit [23].

4.2 Guidelines for Cancer Pain Management in Acute Inpatient Palliative Care Setting

Some with cancer pain need hospitalisation in an acute inpatient palliative care unit for severe pain. In an outpatient and a home setting, fast opioid titration, using complex drugs like Methadone, managing pain crisis, neuromodulation of and interventional techniques are not feasible [24]. Quick oral opioid dose adjustments alongside adjuvants are recommended for uncontrolled pain. Interventions meant to modify the amendable cause of cancer pain is achieved using radiation therapy, physical medicine, correcting high calcium, etc., which is only possible during the inpatient admission. The crisis pain is managed using parenteral opioid trial followed by continuous opioid infusion [25]. The opioid infusions are changed to oral and transdermal medications when adequate pain relief is achieved. The patients with crisis nerve-related pain get intravenous lignocaine or ketamine boluses followed by continuous doses until neuromodulation is accomplished. Inpatient admission is needed to adjust the doses of drugs like methadone used for mixed nociceptive neuropathic cancer pain [26]. Interventional pain management procedures are used in the setting of cancer pain, where adequate pain relief is not achieved with strong opioids [27].

4.3 Guidelines for Cancer Pain Management in Home-Based Palliative Care Setting

In a home-based care setting, the nurses and primary physicians assess cancer pain with restricted contribution from the specialist physicians. These evaluations are intermittently done, which leads to poorly controlled pain, insomnia, anxiety, low mood, frequent hospitalisations, high cost and diminished quality of life [28]. They are prone to polypharmacy, excessive over the counter unprescribed medication use and detrimental side effects of the analgesics [29].

They could be managed in similar lines to outpatients using the algorithm of analgesic step ladder [21]. Furthermore, they should get pain self-reporting guide and pain journals for detailing pain scores and other pain-related specifics. They should also receive medication book for recording daily use of background painkillers and breakthrough dosages. It is also suggested to provide pre-emptive analgesic instructions in certain cancer patients in expectation of rapid change in patient's pain and circumstance [30]. They are directed to get the analgesic drugs from the hospitals or general practitioners before they expend their medicines. They are also connected to local dispensary and their GPs to guarantee sufficient continuous supply of analgesics.

4.4 Guidelines for Cancer Pain Management in Hospice and End-of-Life Care Patients

Pain is often a unseen cause of suffering and distress during end of life as patients at their end of life might not be able to articulate pain or have a level of cognitive loss that could hinder pain expression [31]. Misconstructions about pain at end of life, suitability and adverse effects of analgesics, pain underreporting and intricate presentation of pain at end of life could constraint use of analgesics [32]. Doctors often lack proficiencies in recognizing and evaluating pain in patients at end of life with cognitive loss. They also lack skills in deciding suitable analgesics, route, adjustment and using breakthrough analgesics [33]. Patients during their end-of-life face several symptoms at end of life. The quality of life and death is an aggregate result of symptom control and managing psychosocial issues [34]. The research has shown that pain control at end of life is lacking, and unmitigated pain could corrode the self-worth and well-being at end of life [35].

In a cancer setting, for patients at end of life, the pain should be evaluated at least daily. The pain must be expected, and a pre-emptive treatment ought to be offered to all the patients in a hospice or in a hospital for end-of-life care. Besides, doctors should be skilled in evaluating patients with pain who are incapable of articulating pain or has cognitive loss [36]. The doctors should guarantee access and obtainability of all drugs needed for pain management. Painkillers and their doses must be based on careful appraisal of patient's pain. Their doses should be proportional to patient's pain and response to medications should be regularly reviewed. Furthermore, even when patient is in end of life, no attempt must be made to give a higher than necessary dose or incorrect quantity. The PRN (SOS) orders ought to be scripted up to cover recurrent pain and breakthrough pain. In the end-of-life situation, the PRN doses must be used freely used and quick modification of doses of background (round the clock) prescription should be done. The route of painkillers provision at end of life might need to be altered to subcutaneous or intravenous route if the patient cannot take the drugs orally [37]. The palliative sedation must be contemplated at end of life if pain becomes intractable to standard analgesics [38].

Nausea and vomiting are common symptoms experienced by patients with advancing cancer. It may be due to anticancer therapy, drugs or bowel obstruction. It is important to identify the receptor which is being stimulated, so as to treat appropriately. Some general guidelines are to reverse the causes where feasible, check plasma levels of creatinine, digoxin, calcium and rationale prescribing of the drug according to the receptor involved by the inciting cause.

Constipation is common in patients with advanced cancer due to prolonged immobility in patients with advancing cancers, loss of appetite with dehydration and lack of privacy to use toilet and drugs. The non-drug measures like increasing oral intake, encouraging fluids, mobilizing patient where feasible and providing privacy and access to toilet. Generally, a combination of softeners and stimulants are the common pharmacological treatment used in patients with advanced cancer.

Anorexia is the loss of appetite or desire to eat. Cachexia is an involuntary, ongoing loss of bodyweight (>5%) in the last 1–2 months. Could be accompanied by other factors like anorexia, muscle strength decline or inflammation. In patients with significant fluid retention, large tumour mass or obesity, significant muscle wasting may occur in the absence of weight loss. Corticosteroids and progestational agents are often used to help anorexia.

Fatigue is easy tiring and reduced capacity to maintain performance. It is often accompanied by generalised weakness, sensation of difficulty in initiating a certain activity, mental fatigue, defined as the presence of impaired mental concentration, loss of memory and emotional lability. Along with corticosteroids and progestational agents, methylphenidate and modafinil help patients with cancer-associated fatigue.

Breathlessness is a common in patients with advanced malignancy. It may be due to primary carcinoma of lung or mediastinal tumours causing airway obstruction, lymphangitis carcinomatosis, lung metastasis, pleural or pericardial effusion or systemic causes like anaemia. These patients are managed by correcting the cause and low-dose morphine for chronic refractory breathlessness.

Delirium is a common symptom encountered in patients with advanced disease, especially when entering terminal phase. It is distressing both to patients and family members. Management involves reversing the causes like dehydration, hypercalcaemia, bladder or bowel distension, maximising non pharmacological interventions like safe environment, quiet room, familiar professional staff and using typical anti-psychotics like haloperidol or atypical anti-psychotics like quetiapine, risperidone or olanzapine.

5 Psychosocial Aspects of Palliative Care

A comprehensive psychological assessment is integral in the management plan of patients with advanced cancer. The assessment process has to be conducted with empathy, maintaining privacy and confidentiality along with unconditional positive regard and acceptance. Factors to be assessed include patient's perception or awareness of diagnosis and prognosis, current mood symptoms like depression or anxiety, demoralization, presence of sleep and appetite disturbances, fatigue and sense of well-being [39, 40].

The person's journey through different phases of life, significant life events, presence of stressors other than advanced life-limiting illness and sources of interpersonal support are to be noted. Appreciating the person's illness beliefs, illness behaviour and coping styles will help in developing a comprehensive management plan. The presence of personal or family pre-existing psychological issues/functioning or psychiatric disorders are essential to note. The psychological assessment, in any setting—outpatient clinic, inpatient wards or home/respite/hospice care, includes communication related issues like awareness and awareness of diagnosis and prognosis, presence of collusion and denial. Psychological issues of loss, grief, role changes, sleep disturbances, fatigue and quality of life have to be explored. Impact on mood, and presence of depression, anxiety and post-traumatic stress have to be looked for. Various diagnostic instruments can/should be used for assessment of important clinical disorders like depression, anxiety and delirium, which are common in palliative and hospice care settings. Various tools can be used for, e.g. Distress Thermometer and Problem Check List (DT/PCL), Hospital Anxiety and Depression Scale (HADS), Edmonton Symptom Assessment Scale (ESAS), Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), Spiritual Needs Inventory, Beliefs and Values Scale and Palliative Outcome Scale (POS) [4, 6]. Screening and assessment for delirium on can be done by Memorial Delirium Assessment Scale (MDAS) and Nurse Delirium Scale (NDS) [41].

It is equally important to assess the caregivers' quality of life as it has been reported that the caregiving burden can increase as the patient's disease progresses. The mental health and coping of caregivers are essential components of the comprehensive assessment. Family caregivers can experience even greater distress than that of their patients. Family functioning and relationship are predictors of complicated bereavement process. A thorough mental state examination is done to help in identifying affective and anxiety disorders, delirium and cognitive deficits. Individual and family coping, sources of interpersonal support and family cohesion or conflicts are recognized in a well conducted and detailed patient and caregiver interview [42].

Holistic care integrates needs of family and patient as a unit. Often the family has been decimated with the expenses of the cancer therapy. The social worker needs to assess economic status of family, home environment along with social support systems. The economic, medical, nursing and educational needs of the family are assessed.

Spiritual distress assessment has these primary objectives:

- Develop a therapeutic bond with the patient in a clinical setting
- Recognise spiritual issues and confirm, explicate or arrive at a spiritual diagnosis
- Formulate a spiritual care plan that can be shared with the team

For assessment, the FICA scale has proved to be the most useful.

F—Faith and belief—Do you have spiritual beliefs that help you cope with stress?
I—Importance: "What importance does your spirituality have in your life?"
C—Community: "Are you part of a spiritual or religious community? Is this of support to you, and how?"
A—Address: "How would you like me, your health care provider, to address these issues in your health care?"

6 Ethics of Palliative Care

This is one of the most imperative yet difficult areas in palliative care. The four major principles that govern ethics are autonomy, non-maleficence, beneficence and justice. During this time of suffering, conflict arises mainly due to lack of communication between patient's family and professionals. Given the finality of the life-limiting illness; if patient autonomy is respected and patient has a chance at 'decision making' early in the trajectory of an advancing cancer, should there be any conflict? If 'quality of life' is paramount, rather than prolonging unnecessary suffering, then can allowing a patient to die in a hospital or at home, surrounded by loved ones, be considered as beneficence rather than maleficence? This also mirrors the Hippocratic Oath of always working in the best interest of the patient. Withholding unnecessary interventions or withdrawing of the same, when they are not working, is understanding the concept of medical futility. This could hold true for mechanical ventilation, artificial nutrition and hydration, CPR and many other issues. Conflicts arise when patients are referred late in the trajectory of illness, when next of kin is not properly identified, the patient is not mentally competent etc. Constant, consistent and competent communication should be able to resolve conflicts. Physicians should have recourse to other experts in the field, hospital administrators and ethics committees, lastly the courts, to resolve ethical dilemmas and conflicts; this unfortunately can lead to waste of precious time while patient is in the terminal phase in an ICU. It is also incumbent on doctors to respect other ethical issues like duty to alleviate suffering, respect for individual, utility and human rights.

Respecting patient's right to decision making cannot in any way be construed as euthanasia or physician-assisted suicide; these are deliberate acts to end the life of a patient and palliative care physicians condemn such acts. On 10 March 2018, the Supreme Court of India verdict stated that right to life, including the right to die with dignity is upheld, as part of an individual's constitutional right, under Article 21 of the Indian Constitution. This followed the Mumbai High court judgement on the Right to Die with Dignity petition, regarding Aruna Shanbaug, a nurse who lay in a permanent vegetative state at the KEM hospital for over four decades. The learned judges also stated that an adult conscious human being, is fully entitled to refuse medical treatment and may decide to embrace death in a natural way. This is very much in tune with the 'Principles of Palliative Care'. Moreover, the court accepted the validity of advanced directives where an individual can exercise his/her autonomy on the extent of medical intervention that he/she wishes to allow upon his own body at a future date, when he may not be in a position to specify his medical wishes. This would be needed to be upheld both by medical professionals and the next of kin. However, the downside of this verdict, was in the terminology, i.e. that limitation of such life sustaining treatment be termed as 'passive euthanasia'. This is an inappropriate use of the nomenclature, which does not exist in the medical dictionary. Following this landmark judgment, On 12 March 2018, the Indian Council of Medical Research (ICMR) commission released a report with 25 definitions regarding limitation of life-sustaining treatment and providing palliative care at the end of life. The purpose of this report was to facilitate discussion, preparation of guidelines and framing of laws, relating to the treatment limitation and providing palliative care at end of life. The Ministry of Health and family Welfare, along with ICMR and working on developing an Advanced Directive Health Care form.

7 End-of-Life Care and Bereavement Support

An excellent end-of-life care is a person focussed, tailored view of 'Good Death', which incorporates all features of wide-ranging care of an individual at his or her end of life. It involves (1) pertinency to any individual, any place and any disease; (2) respite from physical, emotional, social, spiritual and existential issues; (3) dying at the favoured place of choice and getting suitable care by a skilled health care provider and (4) general access to palliative care at end of life and each person having access to privacy, serene and dignified death [43–45].

Qualitative research of bereaved family/caregiver suggested that end of life their patients experienced (1) inadequate symptom control; (2) partial health related communication; (3) absence of skilled health care resources to provide end-of-life care; (4) non-existence of rounded care; (5) requests of desired place of death not achieved; (6) detached equipment loaded end-of-life care and (7) delayed palliative care referrals. These were important barriers that hindered quality end-of-life care [46–49].

Research on hospital end-of-life care practices showed that (1) prolongation of disease directed treatments until last weeks of life; (2) needless life-sustaining measures; (3) delayed referral to palliative and supportive care services and (4) absence of advanced care planning and nonexistence of anticipatory directives for end of life. These were the key barriers that hindered quality end-of-life care [50–53].

Quality of Death (QOD) Hospice scale, Quality of death and dying (QODD), Care Quality Commission (CQC) review, family assessment of treatment of end of life (FATE) and quality of end-of-life care and satisfaction with treatment (QUEST) are some of the validated tools that measures gaps in quality end-of-life care. These are intended to gauge views on quality of end-of-life care by qualitative interviewing bereaved family caregivers. Quality of death could also be known by reviewing hospital end-of-life care practices through prospective and retrospective research studies [52, 54–57].

The End-of-Life Care in India Taskforce (ELICIT) is constituted by the IAPC in collaboration with Indian Society of Critical Care Medicine and Indian Academy of Neurology. This team is functional concerning a strong ethical and legal structure for enabling good end-of-life care. The end-of-life care consortium was created after the 2010 quality of death report by Lien foundation to foster and support end-of-life care in India. The important purpose was to develop position statement, policy guidelines, impact policy creators and facilitate end-of-life care knowledge among health care providers and public. In September 2014, a position statement [58] and policy guidelines [59] was published. End-of-life care awareness initiatives were commenced across India with the help of CMEs and Webinars. The association had numerous meetings with the National Accreditation Board of Hospitals (NABH) and was effective in introducing crucial modifications to NABH manual concerning end of end-of-life care. To enable end-of-life care delivery throughout India, a meeting by the International Collaborative on best care of the dying was conducted at the Bangalore Baptist Hospital. Bengaluru. Several participants from many organizations involved in palliative care across India, attended the program. The purpose of this program was to propagate information and advance end-of-life care practices across India.

In aftermath of modification of National Accreditation Board of Hospital (NABH) manual, the Quality Council of India invited delegates of Indian Society of Critical Care Medicine (ISCCM) and Indian Association of Palliative Care (IAPC) to offer ideas for restructuring COP 20.0 item of

2011 NABH accreditation manual, which deals with assessing end-of-life care delivered in Indian Hospitals. The delegates of both the associations met the members of quality council of India on 17 July 2015. A form was consequently developed based on IAPC consensus position statement on end-of-life care policy for dying [59], ISCCM and IAPC joint position statement on end-of-life care policy [59] and NABH COP 20.0 items of NABH Manual, 3rd Edition. Professional views of members for both the society/association were pursued and integrated. To offer quality end-of-life care, it is crucial that standards of end-of-life care as endorsed by suitable establishments are applied, and application process is supervised by various national and international accreditation agencies. Therefore, National Accreditation Board for Hospitals (NABH) and Health Care Providers COP 19 of the NABH 2016 document were developed to enable accreditation of hospitals in India. Nevertheless, most often, these guidelines are limited to paper and truthfully end-of-life care practices are never assessed. This is because these accreditors assess presence of a document not its execution or practice. The auditors themselves have a very incomplete understanding of end-of-life care and are do not have the expertise to carry out these audits.

Recently, the Indian Council of Medical Research (ICMR) in collaboration with ISCCM, IAPC and ELICIT has developed the process of creating uniform end-of-life care definitions, which is already published.

8 Paediatric Palliative Care

When children are diagnosed with a life-limiting condition, it is an extremely harrowing situation where contrary to the normal course of life and death, a beloved child is passing on before the parents. The feelings of frustration and helplessness are not only with the parents and siblings but with the team as well.

Common conditions in paediatric palliative care are grouped under four main headings:

1. Life-threatening conditions for which curative treatment may be feasible but can fail, e.g. cancer, organ failure.
2. Conditions were premature death is inevitable but life may be prolonged, e.g. cystic fibrosis.
3. Progressive conditions without curative treatment, e.g. Batten disease.
4. Irreversible but non-progressive conditions where severe disability can lead to premature death, e.g. cerebral palsy.

Unlike cancer, the life of the child suffering from a non-malignant condition could be prolonged, even reaching adulthood. It means many years of support for child, parents, siblings and extended family. The ICPCN estimates that worldwide 20 million children can benefit from palliative care, but access to such services remains an issue.

Some areas in assessment and management unique to children and their families are

Physical
- Age-appropriate clinical assessment (minimal investigations where appropriate)
- Prevention of symptoms whenever feasible
- Use disease-modifying therapy when there will be benefit outweighing toxicity
- Arrange a continuum of care

Psychological and Spiritual
- Age-appropriate assessment and management of psychological and emotional needs
- Counselling—Family as a unit, including siblings

Social
- Identification of financial needs
- Developing social support networks with appropriate referral to other services

Legal
- Identification of legal requirements
- Referral to appropriate legal services
- Documentation of advance directives and patient preferences for care.

8.1 End-of-Life Care

As in adults, the best possible dignity of death should be aimed for whether in an isolated bed in the ward, the home or hospice. Adequate symptom control with essential medication by the appropriate route, surrounded by loved ones. This is best arranged in collaboration with the local GP. A home death would need the arrangement of the death certificate and other formalities.

8.2 Spiritual Care

The essence of paediatric palliative care in India hinges on spirituality. Most people have a firm belief in God and the theory of Karma, which helps in coming to terms with the suffering associated with advancing cancer. The belief that God helps the child to bear the pain and the family the loss when the child is no more; offers a lot of solace to the family. The even more intangible suffering associated with the oft asked question “Why me” by grieving parents about to lose a beloved child is more difficult. While being unable to truly understand having not gone through the trauma ourselves, gentle patient listening with adequate emotional support over a period of time is of some benefit.

8.3 Symptom Management

Largely as in adults. There are certain myths, e.g. babies do not feel pain. These fears need to be allayed and evidence-based medicine practised for effective symptom management. Although many medications are considered not recommended in children, the reality of the situation is that these drugs do not get tested in children. Some drugs are used as 'off label' use after consultation with parents, if no other effective drug is available. Dosage is calculated individually on the BMI or kg body weight. Metabolism of the drugs is quicker in children and sometimes dosages needed to be given more frequently than in adults. Oral route is preferred wherever feasible. Some children have a Hickman or PICC in situ which is useful for continuous medication where oral route is not feasible. S/C route is used rarely and only possible with a syringe driver or pump. IM injections should be used even more rarely.

8.4 Bereavement Support

A vital section of palliative care is provided by all palliative care teams until the next of kin has the ability to move on in life. The grief is felt by 90% of families. Prolonged, delayed or excessive form of depression can have serious effect on life, and prolonged intervention might be necessary. Studies have shown that response too soon by palliative care teams can even be harmful and should be limited for those families manifesting abnormal grief. Right timing of a bereavement support is researched, and there are diverging views in literature [60].

9 Challenges in Delivering Palliative Care in India

At present, there is no national palliative care policy and only two states in India, Maharashtra and Kerala have state palliative care policy. According to 2015 Quality of Death report ranking, in India, the capacity to deliver palliative care is scored as 0.6/100, i.e. only 0.4% of the population in India have access to palliative care. At present in India, there is only availability of one full time practicing specialist palliative care physician per one million population [61].

Access to oral morphine might be a marker of palliative care delivery. Approximately 0.4% of the patients in India have access to oral morphine [62]. In 2008, India used a quantity of morphine adequate for around 40,000 patients experiencing moderate to severe cancer pain [63]. Morphine is encompassed in the National Essential Medicine List. However, its accessibility remains sparse [64]. The morphine and morphine comparable opioid consumption in India at present is <1 mg per capita [65]. Although there was a recent amendment to Narcotic Drugs and Psychotropic Substance Act in 2014, its execution remains challenging [66].

India has a roughly 100 million elderly population currently, which is projected to rise to 324 million by 2050, forming 20% of the whole population. It is anticipated that 60% of elderly patients might have cancer [67]. Surveillance Epidemiology and End Results (SEER) study of the National Cancer Institute in the USA indicates that cancer is 11 times more probable to occur in people over 65 years as matched to their younger counterparts [68]. An ICMR population-based cancer registry report demonstrated that the frequency of cancer patients in India above the age of 60 is expected to touch more than one million by 2021 [69].

The present legal position in India is only limited to passive euthanasia, and there is no well-defined legal framework or policies to support the clinicians on palliative and end-of-life care. Non-existent national palliative care policy and equivocal legal positions are the most important disadvantages to the delivery of efficient palliative care [70].

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Clinical Pharmacology in Oncology

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Abbreviations

6-MP	6-mercaptopurine
ABW	Actual body weight
AUC	Area under the concentration–time curve
CEA	Cost-effective analysis
CLL	Chronic lymphocytic leukaemia
$C_{\max}$	Maximum plasma drug concentration
CrCl	Creatine clearance
CUA	Cost–utility analysis
DDI	Drug–drug interactions
DPD	Dihydropyrimidine dehydrogenase
ECG	Electrocardiogram
H2A	H_2 receptor antagonist
HRQOL	Health-related quality of life
KDIGO	Kidney Disease: Improving Global Outcomes
MTHFR	Methylenetetrahydrofolate reductase
NSCLC	Non-small cell lung cancer
PD	Pharmacodynamic
PE	Pharmacoeconomics
PK	Pharmacokinetic
pop-PK	Population PK/PD analysis modelling
PPI	Proton pump inhibitors
QALY	Quality adjusted life years
QTc	Corrected QT interval
SrCr	Serum creatinine
TDM	Therapeutic drug monitoring
TKI	Tyrosine kinase inhibitor
TPMT	Thiopurine methyltransferase

1 Introduction to Clinical Pharmacology

Clinical pharmacology deals with the relationship between drugs and individuals and helps in rational prescribing of drugs to treat diseases, alleviate symptoms and prevent adverse effects. Benefits and risks in the form of adverse effects of a drug or undesirable drug interactions should be weighed against each other while prescribing the drugs. Also, the benefits of prescribing a drug should be justified by the cost per unit gain in health metric. As we enter into the era of personalized medicine, the notion 'one size fits all' is gradually replaced by the paradigm of individualized dosing. Thus, the field of modern-day clinical pharmacology draws inspiration from our knowledge and understanding of pharmacokinetics, pharmacodynamics, pharmacogenetics and pharmacoeconomics.

Some important definitions of terms commonly used in clinical pharmacology are provided below:

Clinical pharmacokinetics: Pharmacokinetics deals with 'what body does to the drug' in terms of absorption, distribution, metabolism and excretion. Application of pharmacokinetics in therapeutics is called clinical pharmacokinetics.

Clinical pharmacodynamics: The processes such as receptor binding and chemical interactions by which a drug can affect the physiology, biochemistry and molecular pathways of health and disease is known as clinical pharmacodynamics.

Therapeutic index: It is the ratio of the dose of a drug that causes the therapeutic effect to the dose that causes toxicity. It is also referred to as therapeutic ratio.

Therapeutic window: The dose range across which the therapeutic response is observed without significant toxicity is called the therapeutic window. It is the difference between minimum effective concentrations and minimum toxic concentration.

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Clinical toxicology: The branch of clinical pharmacology dealing with the prevention and treatment of adverse effects caused by drugs and toxins is called clinical toxicology.

2 Pharmacokinetics

Pharmacokinetics describes the concentration–time profile of a drug. Important processes involved in pharmacokinetics are absorption, distribution and the two routes of drug elimination—metabolism and elimination. They are known by the acronym ADME. Distribution, metabolism and excretion are sometimes collectively referred to as drug disposition.

2.1 Absorption

The movement of a drug from the site of administration into the bloodstream is called absorption. This process is involved in all routes of administration other than intravenous route. The drug molecules must cross tissue membranes (e.g. subcutaneous tissue, skin, gut epithelium and capillary wall) to enter the blood. The extent to which a drug is absorbed into the systemic circulation is called *bioavailability*.

2.2 Distribution

Distribution is defined as the movement of a drug from one location in the body to another location in a reversible fashion. Following systemic absorption, movement of drug molecules across capillary walls to enter the tissues and subsequently the cells by crossing the cell membrane is essential for pharmacological effects of a drug.

2.3 Metabolism

The process by which drugs are biotransformed from a lipid-soluble form suitable for absorption and distribution to a more water-soluble form that is suitable for excretion is known as metabolism. Metabolism primarily occurs in the liver, gut wall, kidney and skin.

Drug metabolism occurs in two phases:

Phase I—These reactions involve either adding or unmasking a functional group to the drug and thereby making it more polar. Functional groups such as -OH, -NH_2, -SH prepare the drug molecule for phase II reactions described below. Phase 1 reaction usually proceed by oxidation reactions catalysed by members of the cytochrome P450 family of enzymes found in the hepatocytes' smooth endoplasmic reticulum. Majority of products of phase I metabolism are pharmacologically inactive; however, some retain activity to varying degrees and some exhibit activity that the parent drug lacked.

Phase II—The phase I metabolites (or in some cases, unchanged drug) undergo covalent linkage with endogenous substrates such as glucuronide, sulphate, glutathione, acetate and methyl groups to form an inactive compound which is more water soluble and gets excreted easily.

2.4 Elimination

Elimination is an irreversible process by which the drug is removed from the body. Drugs with a low molecular weight that are sufficiently water soluble are eliminated in the urine. Only the unbound concentration of the drug is filtered by the glomeruli and is available for elimination. Drugs with high molecular weight are preferably excreted via the faecal route after conjugation in the liver. Depending on their lipid solubility, certain unchanged drug or metabolites will be reabsorbed and re-enter the blood stream via the portal vein. This recycling between the liver, bile, gut and portal vein is known as *enterohepatic circulation*.

2.5 Concentration–Time Relationship

Usually, following drug administration, absorption and distribution take place relatively faster, and elimination happens at a slower pace. Pharmacokinetic relationship can be described by plotting the plasma drug concentration against time since administration. While majority of the drugs have first-order elimination kinetics (a constant fraction of the substance being removed over time), a small minority exhibit zero-order kinetics (a constant amount of drug is removed over a given time). The concentrations of the drugs that follow first-order kinetics at different time points can be predicted based on their half-life—the time taken for the drug concentration to halve. Furthermore, the relationship between concentration and time varies based on the route of administration too. For example, duration of exposure is longer when a drug is administered intravenously than when it is administered orally.

2.6 Repeated Drug Administration

Drugs are effectively removed from the body within hours or days after administration by metabolism and excretion. To ensure that the drug concentrations at the site of action remains effective, prescribers have to plan repeated drug administration. Quite often, the frequency of dosing, the time taken to achieve steady state concentration, and the time required for the drug to disappear after treatment is stopped will be determined by the pharmacokinetic characteristics of individual drugs. Thus, some drugs with short half-lives have to be administered continuously by intravenous infusion, while others with long half-lives require loading doses to hasten their clinical effects.

2.6.1 Steady State

Steady state concentration is said to be achieved when the dosing rate equals the rate of elimination. Chronic disease situations require the systemic drug levels to reach target steady state levels for maximum safety and efficacy. The time taken for a drug to reach steady state is a function of the elimination half-life of the drug. It takes approximately 5–7 half-lives of the drug to achieve steady state concentrations (Fig. 1).

Maintenance Dose The maintenance doses are calculated in such a way so as to maintain steady state concentrations, i.e. just enough drug is given in so as to replace the drug eliminated in preceding dose. Clearance of the drug is the most important parameter to be considered for maintenance dose.

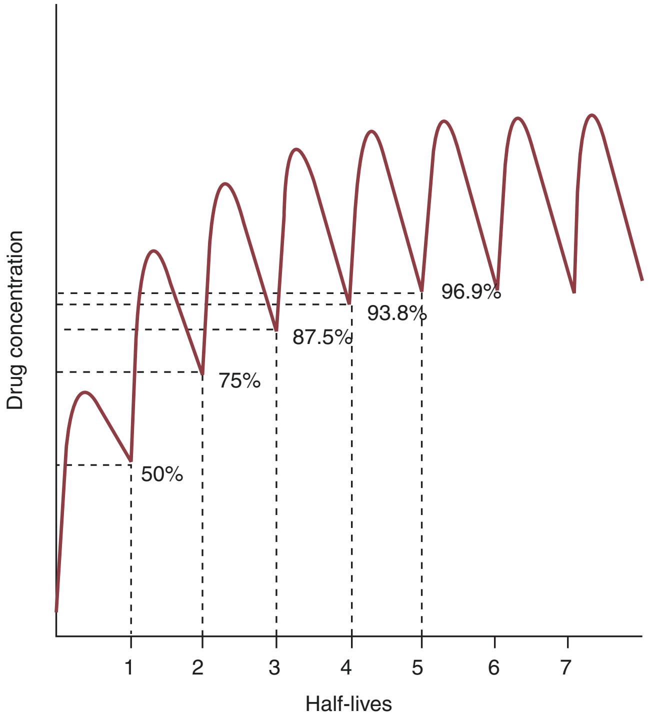

Fig. 1 Steady state: The graph depicts the number of half-lives required to achieve steady state concentration following repeated administration of a drug

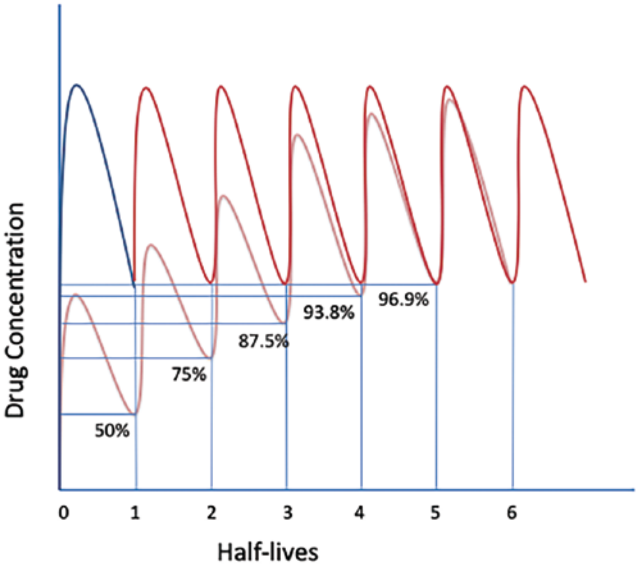

Fig. 2 Loading dose and maintenance dose: The figure demonstrates the importance of loading dose (blue curve) in achieving steady state rapidly. In contrast, it takes 5–6 half-lives to achieve steady state in the absence of a loading dose (red curve). Once achieved, steady state can be maintained using maintenance doses

Drugs which are eliminated rapidly because of short half-life, achieve steady state in a relatively short time. On the other hand, drugs that are eliminated slowly could require days or weeks to achieve steady state. However, if the therapeutic effects are needed quickly (pain relief, antibacterial effect, etc.) and the drug has a long half-life, one can use a loading dose to achieve therapeutic levels on the first dose.

Loading Dose The loading dose rapidly achieves the target concentration necessary to provide the desired therapeutic effect (Fig. 2). The volume of distribution of the drug plays an important role in the calculation of loading dose.

The relationship between the loading dose and volume of distribution (Vd) is given by the equation.

$$\text{Loading dose} = C_{\mathrm{T}} \times \mathrm{Vd}$$

where C_{T} is the target plasma concentration.

The loading dose should be twice the maintenance dose whenever the dosing interval is similar to the half-life of the drug. This is explained by the fact that after one half-life the drug concentration will have dropped by half, thus ‘topping up’ with another maintenance dose will bring it back to the same peak concentration as the loading dose.

3 Pharmacodynamics

Generally, drugs interact with receptors located either on the cell membrane or within the cell and activates them leading to a biological response. The response is proportional to the concentration of the activating drug (the *agonist*). A dose–response curve is used to depict the relationship between the drug dose (or concentration) and its effect [1]. The maximum biological response that a drug can achieve is called *efficacy*, and the amount of the drug required to achieve a response is called *potency* of the drug (Fig. 3).

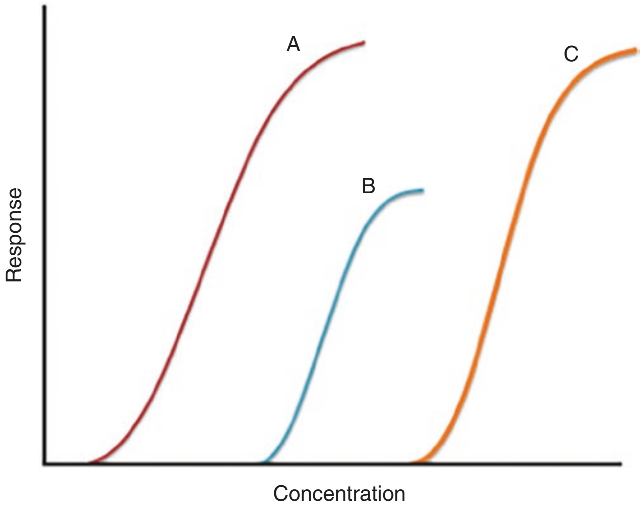

Fig. 3 Potency and efficacy: Concentration–response plots of three drugs A, B and C are shown. Drug B vs. Drug A: A downward and outward shift is seen in the dose–response curve of drug B. This suggest that drug B is less potent and less efficacious compared to drug A. Drug C vs. Drug A: Only an outward shift is seen in the dose–response curve of drug C. This suggest drug C is less potent but equally efficacious as drug A. Drug C vs. Drug B: An outward and upward shift is seen in the dose–response curve of drug C. This suggest drug C is less potent but more efficacious than drug B

4 Interindividual Variability

4.1 Pharmacodynamics

Variation in response to variation in target receptorsin terms of structure and number, receptor coupling mechanisms or a result of physiological changes in target organs resulting from genetic differences, health status or age of the individual. For example, mutations in the kinase domain of epidermal growth factor receptors (e.g. ErbB1-L858R) in some lung cancer patients are known to confer higher affinity and sensitivity to kinase inhibitors such as gefitinib [2].

4.2 Pharmacokinetics

The variations in the drug concentrations achieved by equivalent doses are attributed to various factors which affect the absorption, metabolism and excretion of the drugs. The most important source of such variability in response to a drug is drug metabolism. A high-fat meal corresponds to an 80% increase in the nilotinib levels, the distribution of sorafenib is highly influenced by hypoalbuminemia and variation in cytochrome P450 and ABC transport polymorphism accounts for metabolism of tamoxifen and most other TKIs (sorafenib, gefitinib, imatinib and dasatinib).

4.3 Therapeutic Drug Monitoring (TDM)

TDM entails the measurement and interpretation of drug concentrations in biological fluids in order to individualize patient management. To enhance therapeutic efficacy while minimising unwanted effects, the dose is often modified based on serum/plasma levels. Inter-patient variability in pharmacokinetics of anticancer drugs contributes to the inter-individual differences in response to these drug [3, 4].

Table 1 Drugs for which therapeutic monitoring is indicated in oncology

Drug	Concentration	Need for TDM	Level of evidence
Methotrexate	<0.5–1.0 µmol/L, 48 h after high-dose methotrexate	Methotrexate displays high variability in total body clearance (40–400 mL/min)	Level 2
Busulfan	Target 6 h AUC is 900–1500 µmol min/L	High intra- and interindividual variability	Level 1
5-Flurouracil	Target AUC at steady-state 18–28 mg h/L	Variable systemic clearance (approx. 5 L/min variable up to 100-fold)	Level 1
Mitotane	Target trough concentrations: 14–20 mg/L	Higher exposure associated with risk of neurological toxicity	Level 2

AUC area under the concentration–time curve

Individuals who metabolize and excrete the active substance slowly have larger systemic exposures and vice versa (e.g. UGT1A1 activity and the risk of irinotecan induced myelosuppression).

TDM is routinely practised for select antibiotics, antifungals, antiepileptics, immunosuppressive agents, neuroleptics and antiretroviral drugs. Important considerations for TDM of a drug include the absence of an easily measurable biomarker for drug effect(s), need for long-term therapy, presence of a validated sensitive bioanalytical method for the drug, significant interindividual and relatively low intra-individual variability, narrow therapeutic index, presence of a defined and consistent exposure–response (efficacy/toxicity) relationship and a feasible dose-adaptation strategy [5].

In oncology, TDM is indicated for methotrexate, busulfan, 5-flurouracil, carboplatin, mitotane and imatinib. Some of the novel-targeted drugs belonging to the family of tyrosine kinase inhibitors and monoclonal antibodies have significant interpatient variability in addition to having exposure–effect relationships for response and/or toxicity. Thus, more candidate drugs are likely to emerge in future for TDM including 13-*cis*-retinoic acid, sunitinib, sorafenib, nilotinib, dasatinib, cetuximab, rituximab and bevacizumab [6]. Table 1 lists drugs for which therapeutic monitoring is indicated in oncology.

5 Risk Versus Benefit

Anticancer drugs have off-target effects on rapidly proliferating cells including the bone marrow, gastrointestinal tract, hair follicle and gonads. Common toxicities encountered therefore include neutropenia, thrombocytopenia, diarrhoea, alopecia and infertility, although other organs may also be affected by specific drugs such as doxorubicin-induced cardiac toxicity and bleomycin-induced pulmonary fibrosis. Consequently, majority of cytotoxic drugs are having narrow therapeutic index. The graphical representation of therapeutic index is shown in Fig. 4.

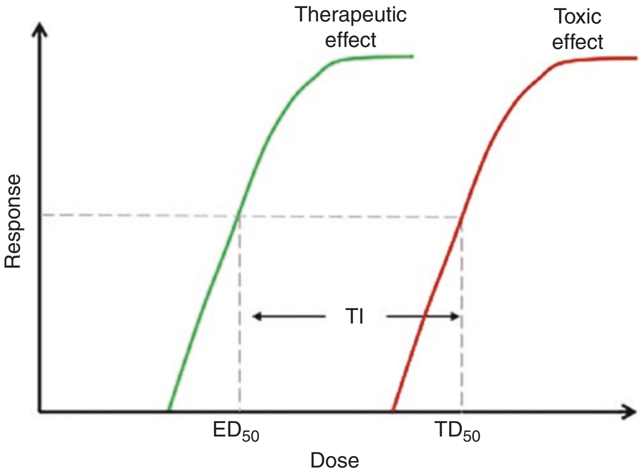

Fig. 4 Therapeutic index: Dose–response curves for efficacy (green curve) and toxicity (red curve) are shown. ED_{50} and TD_{50} are the doses that are effective in and toxic to 50% patients respectively. The ratio between the TD_{50} and ED_{50} is the therapeutic index (TI)

6 Pharmacovigilance

Pharmacovigilance, as defined by WHO, is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug-related problem [7]. The high incidence of toxicities and narrow therapeutic window of antineoplastic agents necessitates constant monitoring of adverse events long after a drug is approved for human use. Clinical trials are not able to uncover the rare and late toxicities of new drugs, and hence routine surveillance of these adverse events is carried out during the post-marketing period [8]. The risk associate with any treatment has to be weighed against its intended benefits. Hence, while neutropenia may not be an acceptable toxicity of a drug used for the treatment of minor ailments, it is generally accepted for anticancer agents. Pharmacovigilance activities in the past have led to black box warnings (e.g. sunitinib and pazopanib-induced hepatotoxicity, embryo–fetal death caused by vismodegib, ponatinib-induced arterial occlusions) and even recall of drugs (e.g. gemtuzumab indicated for acute myeloid leukaemia was withdrawn in the US due to increase in the risk of death; trovafloxacin, an antibiotic, was withdrawn from EU and US markets due to increase in the risk of liver failure; phenformin an antidiabetic agent was withdrawn due to risk of severe lactic acidosis).

7 Drug Interactions

Changes in the safety and efficacy profile of a medication when co-administered with other drugs or in the presence of environmental pollutants or food is known as drug interaction. Approximately one-fifth of all adverse reactions to drugs are due to drug interactions [9]. Drug interaction mostly deals with drug–drug interactions (DDI), but the pharmacokinetics and/or the pharmacodynamics of drugs can be altered by various other substances such as food [10], nutritional supplements [11], formulation excipients and environmental factors (such as cigarette smoking).

Drug interactions can be the result of altered pharmacokinetics, pharmacodynamics or a combination of mechanisms. The alterations in absorption, distribution, metabolism or elimination of one drug by another drug or substances refers to the pharmacokinetic interactions.

When two or more drugs or substances are co-administered together and have similar molecular targets, the additive effects might result in excessive response or toxicity. Similarly, if the drugs have an opposing effect, it can reduce the response to one drug or both drugs. This is known as pharmacodynamic interactions. Table 2 lists clinically significant drug interactions.

Table 2 Clinically significant drug interactions

Anticancer drug	Concomitant drug	Mechanism	Recommendation
Crizotinib, Dasatinib, Erlotinib, Gefitinib, Lapatinib and Pazopanib	Acid suppressive agents (PPIs, H2As and antacids)	The absorption of these TKIs is significantly affected by concomitant use with acid suppressive agents	The combination of acid suppressive agents and TKIs must be avoided, if possible, if not, both drugs must be taken with a significant amount of time in between to prevent any interaction
Axitinib, Crizotinib, Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib, Nilotinib, Pazopanib, Regorafenib, Ruxolitinib, Sunitinib, Vemurafenib	Strong CYP3A4 inhibitors—ketoconazole, itraconazole and voriconazole Strong CYP3A4 inducers—rifampicin and enzalutamide	PK of TKIs (especially $C_{\max}$ and AUC) can be significantly altered by concomitant use with CYP3A4 inhibitors/inducers	In case the combination is used, dose adjustments are highly recommended
Crizotinib, Gefitinib, Lapatinib, Nilotinib, Pazopanib, Sorafenib, Sunitinib, Vandetanib, Vemurafenib, Tamoxifen	QTc interval-prolonging 5HT3 antagonists, antibiotics, ondansetron/granisetron/sotalol/erythromycin/levofloxacin/methadone/risperidone/azithromycin antifungals, and over-the-counter drugs (e.g., domperidone)	The QTc-interval can be significantly prolonged by concomitant use of these drugs	In case the combination is used, ECG should be taken 24–48 h before and 1 week after initiating the therapy
Pazopanib, Sunitinib, Crizotinib, Lapatinib	P-glycoprotein substrates with a narrow therapeutic window (e.g. digoxin, ciclosporin and tacrolimus), lapatinib	P-glycoprotein inhibition increased digoxin AUC by 80% and decreased pazopanib AUC by 59%	In case the combination is used, it should be liberally monitored for, e.g. by therapeutic drug monitoring
Sunitinib, Nilotinib Pazopanib, Lapatinib	Grapefruit juice	Enzymes in grapefruit inhibit CYP450-3A4 associated metabolism	This combination should be avoided
Methotrexate	Prednisolone, Amoxycillin	Prednisolone and penicillin may reduce methotrexate clearance	Close monitoring of serum methotrexate levels is required

PPI proton pump inhibitors, *H2A* H_2 receptor antagonist, *TKIs* tyrosine kinase inhibitors, C_{max} maximum plasma drug concentration, *AUC* area under the concentration–time curve, *QTc* corrected QT interval, *ECG* electrocardiogram

8 Special Population

Liver and kidney are the major organs responsible for the elimination of drugs from the body. Dysfunction of either of these organs can lead to alteration of drug pharmacokinetics. Renal insufficiency is more common among cancer patients compared to the general population. Up to a quarter of cancer patients will have stage 3 or 4 kidney disease at some point during their treatment (i.e., GFR ≤ 60 mL/min) [12]. Cancers that commonly metastasize to the liver such as breast and colorectal cancers are likely to cause hepatic dysfunction [13].

8.1 Dosing Recommendations in Kidney Disease

Renal dysfunction causes a variety of pharmacokinetic alterations like reduced metabolic capacity of the drug, volume of distribution may be affected due to alterations in tissue binding, reduced renal excretion and production of toxic compounds. These alterations in pharmacokinetics necessitate dosage adjustment in renal impairment. Most of the anticancer agents require renal dosage adjustment. According to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice recommendation, dosing in renal impairment should be according to the approved product labelling [14]. Drugs relatively safe in renal impairment are 5-fluorouracil, irinotecan, imatinib, abiraterone, azacitidine, panobinostat, axitinib and idelalisib. Table 3 lists the anticancer drugs for which dosage adjustment is required in renal dysfunction.

8.2 Dosing Recommendations in Hepatic Impairment

In cancer patients, hepatic dysfunction is more common than renal dysfunction. Organ dysfunction can be due to pre-existing diseases such as cirrhosis, metastasis or due to the toxic effects of drugs. Hepatic dysfunction alters drug's pharmacokinetics. The various alterations are rate of drug metabolism, for drugs which are eliminated in the bile or faeces clearance of the drug will be reduced, portal hypertension alters the absorption of the drug and highly albumin bound drugs will have increased free concentrations due to low albumin production by the liver.

Table 3 Drug requiring dose modifications in renal disease

Drugs	Dose adjustment in renal impairment [15–17]
Bendamustine	If CrCl <40 mL/min—do not use
Bleomycin	• CrCl 40–50 mL/min—reduce dose by 30% • CrCl 30–40 mL/min—reduce dose by 40% • CrCl 20–30 mL/min—reduce dose by 45% • CrCl 10–20 mL/min—reduce dose by 55% • CrCl 5–10 mL/min—reduce dose by 60%
Capecitabine	• CrCl 30–50 mL/min—reduce dose by 25%CrCl <30 mL/min—do not use
Carboplatin	Dose based on Calvert's formula • CrCl <30 mL/min—do not use
Cisplatin	• CrCl 46–60 mL/min—reduce dose by 50% • CrCl 31–45 mL/min—reduce dose by 75% • CrCl <30 mL/min—do not use
Cytarabine	• CrCl 40–60 mL/min – If dose >2 g/m^2/dose—reduce to 1 g/m^2/dose – If dose is 0.75–1 g/m^2/dose—reduce to 0.5 g/m^2/day • CrCl <40 mL/min—25% of full dose – If dose >0.75 g/m^2/dose, give ≤200 mg/m^2/day
Daunorubicin	If SrCr >3 mg/dL—reduce daily dose by 50%
Fludarabine	• CrCl 30–70 mL/min—reduce dose by 50% • CrCl <30 mL/min—do not use
Methotrexate	For low doses (<1 g/m^2) • CrCl 30–60 mL/min—50% of full dose • CrCl <30 mL/min—do not use For high doses—consider TDM
Oxaliplatin	• CrCl >30—No dose reduction • CrCl <30 mL/min—Decrease dose to 65 mg/m^2
Pemetrexed	If CrCl <45 mL/min—do not use
Topotecan	• CrCl 30–60 mL/min—reduce dose by 25% • CrCl 10–30 mL/min—reduce dose by 50% • CrCl <10 mL/min—do not use

CrCl creatine clearance, *SrCr* serum creatinine

Table 4 Drugs requiring dose modifications in hepatic disease

Severity of liver dysfunction	Drugs requiring ≥75% dose reduction or omitting of drug	Drugs requiring 50% dose reduction	Safe drugs
Mild (Bilirubin ULN-2 mg/dL)	Docetaxel Irinotecan Paclitaxel	Vincristine Vinblastine	Gemcitabine[a]
Moderate (Bilirubin 2–3 mg/dL)	–	Doxorubicin Etoposide Vinorelbine	–
Severe (Bilirubin >3 mg/dL)	Doxorubicin[b] Etoposide Vincristine, Vinblastine, Vinorelbine, Imatinib	–	Oxaliplatin Topotecan 5-Fluorouracil, Capecitabine Cyclophosphamide[c]

ULN upper limit of normal

[a] Decrease the dose by 20%, increase gradually

[b] Idarubicin does not require dosage adjustment in hepatic dysfunction; epirubicin requires dose adjustment based on AST (aspartate aminotransferase) elevation. Dose reduction is required by 25%, 50% and 75% when the AST levels are 150–250, 250–500, >500 IU/L, respectively

[c] To be administered at 75% of standard dose

There is no standardized system with which to define liver dysfunction in patients with malignancy. Furthermore, various sources often differ in dosing recommendations, which further complicates management of patients with impaired hepatic function. Table 4 enumerates the dosing recommendations for anticancer drugs for varying degrees of hepatic dysfunction.

8.3 Dose Modifications in Obesity

Obesity is an epidemic which is spreading very fast due to changing lifestyles of people around the world. Metabolic dysregulation is often observed in obesity, leading to increase in circulating levels of insulin, IGF-1, adipokines, cytokines and pro-angiogenic factors, which are known to promote cancer development and progression [18, 19]. It is associated with certain physiological alterations that may have a bearing on drug disposition including decreased cardiac function and tissue perfusion, higher volume of distribution of lipophilic drugs and highly variable creatinine clearance which poses a challenge while dosing chemotherapeutic drugs. Obese individuals have higher total lean body mass, and the volume of distribution of hydrophilic drugs is well correlated than that for lipophilic drugs.

Based on the individual drug characteristics, their levels in the plasma may be much different in obese and non-obese patients with similar tissue concentrations [20]. In the past, several alternative descriptors of weight have been used while calculating the dose of chemotherapeutic drugs in obese cancer patients. These include dose capping, dose banding, flat-fixed dosing and using ideal body weight, adjusted body weight, lean body weight instead of total body weight. Alternatively, restricting the dose by capping BSA to 2 m^2, or increasing the duration between treatments are also practiced for the fear of inducing toxicity. However, recent evidence points at higher treatment failure rates or lower overall survival in obese patients when such dosing strategies are adopted.

The following are a few recommendations from ASCO while managing obese cancer patients [21]:

- Actual body weight should be used for dosing chemotherapeutic drugs. It is particularly important when the goal of treatment is curative.
- Comorbidities should be considered for obese individuals, particularly the choice of chemotherapy which need higher doses and association of toxicities with the comorbid conditions.
- The dose de-escalations due to side effects should be done consistently for both obese and non-obese patients.
- For certain chemotherapeutic drugs, the established dosing regimen should be adhered to irrespective of the BMI. For instance, vincristine dose should not exceed 2 mg per dose, and the maximum lifetime dose of bleomycin should not exceed 400 units because of the risk of neurotoxicity and pulmonary fibrosis, respectively, at higher doses, and carboplatin is always dosed based on kidney functions.

9 Clinical Pharmacology in Drug Development

9.1 Biomarkers

According to the National Cancer Institute, a biomarker is 'a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease' [22]. With improved understanding and interpretation of genomic information, next-generation sequencing data will aid in the choice of drug therapy and dosing regimen in the clinical setting. Importance of molecular targets is exemplified by EGFR. Anti-EGFR-targeted antibodies have shown activity in the treatment of non-small cell lung carcinoma (NSCLC) and in a variety of epithelial tumour types, including head and neck cancers and advanced colorectal cancer. This is also true for other targeted drugs such as crizotinib for ALK gene rearrangements. Biomarkers are broadly classified into pharmacodynamic, predictive and prognostic markers.

9.1.1 Pharmacodynamic Biomarker

A pharmacodynamic (PD) biomarker is used to indicate whether the biological effect has occurred on exposure to a drug. PD markers provide information on the direct pharmacological effect of a drug on its target. In the preclinical development phase, the PD biomarkers are used to design drugs which inhibit specific molecular targets. In clinical trials, PD biomarkers help in optimizing the dose of the drug, by correlating the extent of its modulation with the concentration of drug in tumour or surrogate healthy tissues. Thus, the term optimal biological dose was introduced. For example, dose selection of imatinib in early trials was guided by the inhibition of BCR-ABL tyrosine kinase in circulating peripheral blood leukemic cells [23].

9.1.2 Predictive Biomarker

A predictive biomarker is defined as a marker having the potential to discriminate individuals who are more likely than similar individuals without the marker to experience a favourable or unfavourable effect from exposure to a drug [24]. Biomarker-based study designs are generally proposed for targeted drug therapies. The predictive markers are often co-developed with the drug. For instance, in early clinical trials, the relative expression of the marker in tumor with respect to normal tissue is investigated, and any relevant thresholds of marker positivity are selected for application in later trials. In phase II trials, marker-based subpopulation where efficacy of a targeted therapy is most promising is validated. Phase III trials involves randomized treatment

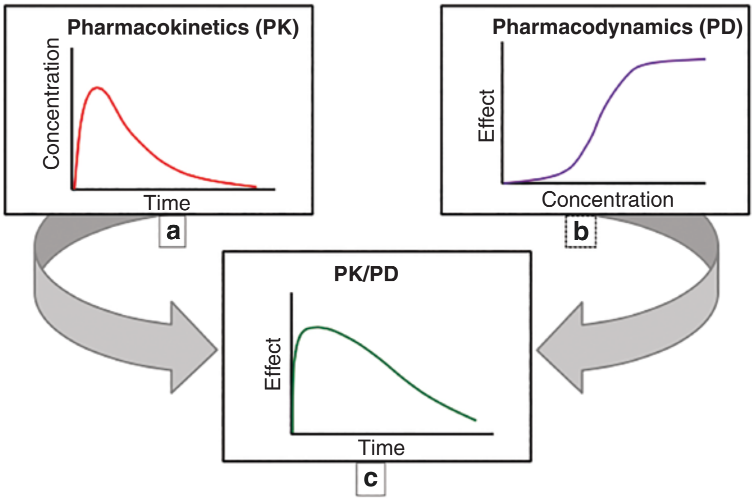

Fig. 5 PK/PD modelling—graphical representation: Pharmacokinetics profiles the change in drug concentration as a function of time (**a**). Pharmacodynamics depicts the change in response as a function of drug concentration (**b**). PK/PD modelling establishes the time course of response with respect to drug administration (**c**). The variability in response and the factors (co-variates) contributing to the variability are quantitatively expressed

comparison in the population believed to benefit from marker directed treatment. For example, BReast CAncer genes 1 and 2 (BRCA1/2) mutations were used as predictive biomarkers in platinum-sensitive ovarian cancer, to identify patients likely to respond to PARP inhibitors [25].

Enrichments Designs

Enrichment is the prospective use of any patient characteristic—demographics, pathophysiologic, historical, genetic and others—to select a population of patients who are more likely to benefit from the drug. Enrichment design is employed primarily in late-phase trials (Phase II or Phase III) and involves enrolling only the biomarker-positive patients and comparing the test drug against the standard treatment only in the biomarker-defined subgroup.

Advantages

- Improved efficiency and feasibility of the trail.
- Enhanced benefit versus risk, especially if the intervention is associated with severe toxicity.
- Efficient in terms of speed and cost.

9.1.3 Prognostic Biomarkers

A prognostic biomarker is a biomarker that is used to predict the likelihood of a clinical event such as recurrence of disease or progression in patients with the disease or medical condition of interest. In clinical trials, prognostic biomarkers define the study population and help in formulating the study objectives. They must be taken into account while analysing the outcomes of a study so as to obtain accurate estimates of the treatment differences and to evaluate results across studies. For example, chromosome 17p deletions and TP53 mutations prognosticate overall survival in chronic lymphocytic leukaemia (CLL) and should be accounted for in the survival analysis of new interventions for CLL in randomized phase 3 clinical trials [26].

9.1.4 PK/PD Modelling (Fig. 5)

The term PK/PD (pharmacokinetic and pharmacodynamic) modelling refers to a data-driven exploratory analysis based on a mathematical/statistical model that quantitatively describes the relationship between drug exposure (PK profile) and response (PD effect). The models are useful to determine how much exposure is needed, and for how long, to exert the desired effect. PK/PD modelling and simulation is a widely used tool in drug development. The models are useful in predicting the pharmacological response at various dosing regimen within a species, and further for upscaling the dose across species.

PK/PD modelling and simulation can make impact at all the stages of drug development. A PD model based on preclinical or biomarker data, or a PK model based on Phase I data are used for designing subsequent phases of clinical trials. In late phase clinical trials, modelling and simulation can be used to assess the impact of covariates such as subgroups, co-morbidities, concomitant medication and pharmacogenetics on the outcome of treatment. Moreover, the data is useful to assess the need for dose adjustment in special populations. In fact, a proactive model-based analysis could alleviate need for additional clinical trials in special populations. For instance, the use of oxcarbazepine monotherapy in children was approved based on PK/PD modelling of data generated in adults.

Population PK/PD analysis modelling (Pop-PK) focuses on merging patient covariates with PK/PD parameters to enable dose individualization. Pop-PK studies identify and quantify sources of variability in the pharmacokinetics of a drug in the patient population. Understanding the patient characteristics that determine the pharmacokinetics can then be used to customize pharmacotherapy. Population modelling typically involves large patient cohorts, but fewer samples (sparse sampling) from each individual and hence it is useful for investigating patient groups or conditions that are not easily studied, such as preterm babies. Not surprisingly, pop-PK is being used more often in drug development. Of note, it is useful when pharmacokinetics of a drug is likely to vary between subgroups of the population.

10 Pharmacoeconomics

Pharmacoeconomics (PE) is a subset of health economics which deals with the measurement and comparison of the costs of drug therapies with one another with a firm focus on healthcare systems and society [27]. A comprehensive PE analysis using economic evaluation methods of healthcare products and services, especially pharmaceuticals, increases their acceptance by healthcare professionals and end users.

10.1 Assessment of Costs and Outcomes

This is the initial step in PE evaluation. Assessing costs and consequences of health care management depends, to a large extent, on the perspective of evaluation. PE evaluation of the value of a product or service can be done from patient, provider, payer and societal perspectives. Patient perspective is particularly important when healthcare is an out-of-pocket expenditure as is the case in most developing countries. Costs can be categorized into various types, as shown in Table 5.

10.1.1 Outcomes

Outcomes of the intervention can be measured in monetary aspects or non-monetary aspects such as QALY (quality adjusted life years) gained. QALY is an indicator of the benefit of health outcomes. For instance, QALY gives as idea about the additional duration of life of a reasonable quality a person might gain out of treatment. It is pertinent to note that outcomes could be either positive or negative. Positive outcomes are a measure of the drug's efficacy, whereas outcomes such as side effects, development of drug resistance and treatment failure are deemed as negative.

10.2 Pharmacoeconomic Evaluation Methods (Fig. 6)

Healthcare provided at a facility should demonstrate a balance of clinical, economic and humanistic outcomes.

Table 5 Categorization of cost

Type of costs	Description	Examples
Direct medical costs	Costs that involve medical products and services used to prevent, detect and/or treat a disease [28]	Drugs, medical supplies and equipment, laboratory and diagnostic tests, hospitalizations and physician visits
Direct non-medical costs	Costs for non-medical services (do not involve purchasing medical services)	Transportation charges to and fro from healthcare facilities and emergency department, child or family care expenses, special nutrition and various other miscellaneous out-of-pocket expenditure
Indirect nonmedical costs	Cost of reduced productivity [27–29]	Loss of Wages due to morbidity and hospitalization
Intangible costs	Non-financial outcomes of disease and medical care [27]	Include pain, suffering, inconvenience and grief and other emotional damage that cannot be measured objectively

PE pharmacoeconomics, *CEA* cost-effective analysis, *CUA* cost utility analysis, *NSCLC* non-small cell lung carcinoma, *QALY* quality-adjusted life years

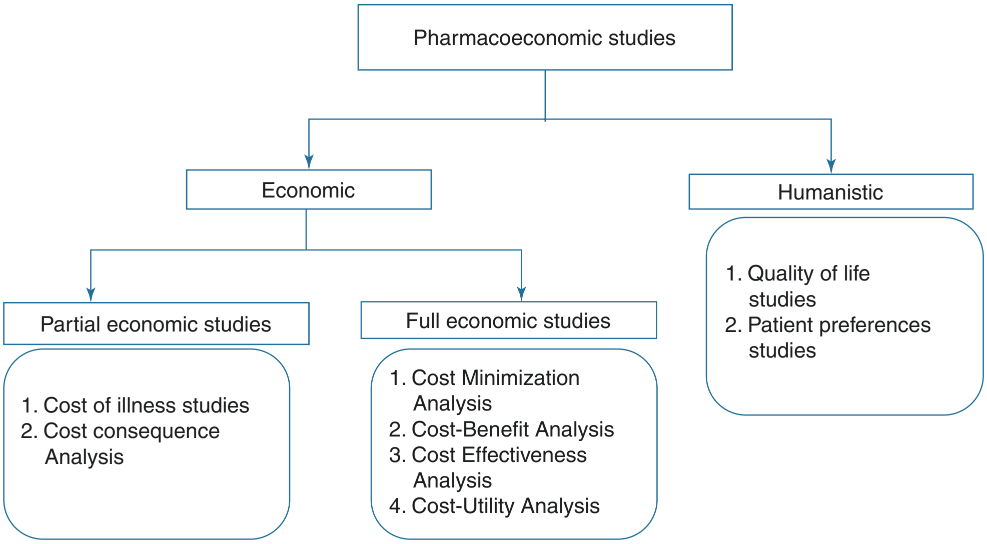
Pharmacoeconomic studies
Economic
Humanistic
1. Quality of life studies
2. Patient preferences studies
Partial economic studies
Full economic studies
1. Cost of illness studies
2. Cost consequence Analysis
1. Cost Minimization Analysis
2. Cost-Benefit Analysis
3. Cost Effectiveness Analysis
4. Cost-Utility Analysis

Fig. 6 Types of pharmacoeconomic analysis

The pharmacoeconomic evaluation techniques can be categorised as economic and humanistic evaluation methods.

10.2.1 Economic Evaluation Methods

Economic evaluation compares alternative courses of action in terms of their costs and consequences [30]. The various types of economic evaluation methods are:

- Cost minimization analysis—the outcome is measured comparing the cost of two or more treatments.
- Cost–benefit analysis—measures both cost and benefit in monetary terms of various interventions.
- Cost-effectiveness analysis—the outcome is measured in natural terms such as life years saved or functional improvements (units of blood sugar or blood pressure).
- Cost-utility analysis—the outcome is based on QALY.

10.2.2 Humanistic Evaluation Methods

Patient preferences, patient satisfaction and health-related quality of life (HRQOL) are becoming increasingly important in pharmacotherapy decisions [31]. These parameters often have physical, emotional and social impact on the patients [30]. HRQOL is usually assessed using patient-completed questionnaires. The questions could be concerned with general well-being or specific for a disease or state of health. Some of the studies that used PE outcome measures are listed in Table 6.

10.3 Pharmacoeconomics in Oncology

Thus, the value of pharmacotherapy could be quantified using the principles of PE by balancing costs and outcomes. It plays a very important role in ensuring the delivery of cost effective and equitable healthcare.

Table 6 Application of cost analysis in oncology

Study description	Cost-effectiveness comparators	Result of PE
CEA for the first-line management of advanced NSCLC of non-squamous cell histology [32]	The various comparator arms used were • Cisplatin and pemetrexed • Cisplatin and gemcitabine • Carboplatin and paclitaxel • Carboplatin, paclitaxel and bevacizumab	Cisplatin and pemetrexed combination was found to be cost effective in this analysis
CEA for the second-line management in NSCLC [33]	Docetaxel was compared with pemetrexed	Docetaxel was found to be most cost effective
CUA of ovarian cancer [34]	Platinum-based chemotherapy versus taxane and other regimens	Platinum-based regimen was found to be better in terms of QALY gained

PE pharmacoeconomics, *CEA* cost-effective analysis, *CUA* cost utility analysis, *NSCLC* non-small cell lung carcinoma, *QALY* quality adjusted life years

11 Personalized Medicine

A drug proven to be efficacious in many patients often fails to work in other patients. The understanding of individual variation in response to a drug helps us to bring the concept of personalized medicine. The latest developments in the field of pharmacogenetics, pharmacogenomics and use of biomarkers help us understand these differences to achieve personalized care. The two approaches to personalized medicine are as follows:

1. Directing targeted agents at unique molecular features of cancer cells
2. Modulating the immune response to tumour through immunotherapy [35]

Table 7 List of drugs exhibiting pharmacogenetic variations

Gene	Encodes	Variants	Affected drugs	Effects
TPMT	TPMT enzyme	*TPMT*3C*, *TPMT*3A*	Thiopurines	TPMT*3A variant is rapidly degraded, leading to prolonged effects of 6-mercaptopurine causing severe myelosuppression Recommendations: Homozygous TPMT—reduce dose by 90%; Heterozygous TPMT—reduce dose based on tolerability
MTHFR (677C>T)	MTHFR enzyme	677 CT 677 TT	Methotrexate	CT has 60% of normal enzyme activity. TT has about 30% of enzyme activity. Carriage of MTHFR 677 T variants has been associated with increased risk for methotrexate toxicities (hematologic, hepatic, and mucosal toxicity)
UGT 1A1	Uridinediphosphate glucuronosyltransferase 1As (UGT 1A1)	UGT 1A1 *28 UGT 1A1 *6	Topotecans—Irinotecan	*28/*28 is associated with higher rates of diarrhoea and febrile neutropenia Recommendations: Homozygous UGT1A1*28—reduce starting dose Used in combination • Weekly dosing—reduce 125 mg/m^2 to 100/75 mg/m^2 • 2-week dosing—reduce 180–120 mg/m^2 Used as monotherapy • Weekly dosing—reduce 125 mg/m^2 to 100/75 mg/m^2 • 3-week dosing—reduce 350–300/250 mg/m^2
CYP2D6	CYP2D6 enzyme	Two or one null allele	Tamoxifen	Reduced activity of CYP2D6 leading to decreased formation of active metabolite—endoxifen leading to inferior outcome in postmenopausal women with early breast cancer
ABCB1	ATP Binding Cassette Subfamily B Member 1	ABCB1 3435 T/T	Taxanes used in breast cancer	Lower toxicity and longer OS
DPD	Dihydropyrimidne dehydrogenase	DPYD*2A DPYD*13	5-Flurouracil	Both variants are associated with higher risk of myelosuppression and neurotoxicity. Recommendations: • Normal DPD activity—No adjustment • Intermediate DPD activity—Reduce dose by 50% • Deficient DPD activity—Use alternative drug

TPMT thiopurine methyltransferase, *6-MP* 6-mercaptopurine, *MTHFR* methylenetetrahydrofolate reductase, *DPD* dihydropyrimidine dehydrogenase

11.1 Pharmacogenetics and Pharmacogenomics

The term pharmacogenetics coined in 1959 defines the science aimed at studying the influence of inherited factors on drug response variability through genetic and pharmacological knowledge. Metabolism of drugs is associated with a variety of genetic polymorphism leading to significant inter-individual variability [36, 37]. Pharmacogenomics is a much broader term that incorporates all genes in the genome that may determine drug response. Table 7 enumerates the effect of pharmacogenetic variations on drug dosing and toxicity.

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Cancer Staging

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Abbreviations

ACR	American College of Radiology
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
ATA	American Thyroid Association
CDC	Centers for Disease Control and Prevention
DLI	Dermal lymphatic invasion
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FNCLCC	The French Federation of Cancer Centers
GIST	Gastrointestinal stromal tumour
IACR	International Association of Cancer Registries
IARC	International Agency for Research on Cancer
IASLC	International Association for the Study of Lung Cancer
ICCR	International Collaboration on Cancer Reporting
LVI	Lymphovascular invasion
MAC	Modified Astler-Coller
NCCN	National Comprehensive Cancer Network
PF	Prognostic factors
PNI	Perineural invasion
UICC	International Union Against Cancer
WHO ICD-O	International Classification of Diseases for Oncology
WHO	World Health Organization

1 Introduction

Cancer staging is the process of determining the extent of cancer, and it reflects the tumour and host relationship. It is an essential part of cancer management that dictates patient care, predicts prognosis, compares oncological outcomes, and improves cancer control. International Union Against Cancer (UICC) and the American Joint Committee on Cancer Staging and End-Stage Reporting (AJCC) are the two separate bodies working parallelly on the TNM staging, which is the most common staging system used among many.

2 Principles and Need of Cancer Staging

The TNM staging system's ultimate aim is to have its universal applicability regardless of a country's level of resources. It is simple, cheap, objective, and does not require very specialised technology.

The following are the objectives of staging [1]:

1. To assign the proper clinical and pathological staging.
2. Based on anatomical and non-anatomic criteria, staging entails stratification into similar groups, which ultimately aid the clinician in prognosticating the disease and planning treatment.
3. To assist in evaluating and stratifying the results of treatment and management of patients.
4. To ensure uniformity in presenting the treatment results concerning oncological outcomes and facilitate better information exchange between centres for treatment-directed research.

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5. To evaluate the results of early detection efforts through population-based screening, surveillance, and through cancer registries.
6. To evaluate treatment guidelines, national cancer control, planning, and research.

2.1 The TNM Oncotaxonomy [2, 3]

The TNM system is an anatomic staging system and specifically applies to solid tumours. It is based on three components: primary tumour (T category), regional lymph nodes (N category), and distant metastasis (M category). The TNM oncotaxonomy provides the necessary structural stencil for the T, N and M and staging system. Haematologic malignancies (leukaemias, lymphomas, and myelomas), by virtue of them not conforming to the pattern of spread characteristic of solid tumours, have separate staging and prognostication systems.

1. *Hollow versus solid organs criteria*:
   There is a fundamental difference between the hollow organs and solid organs, and staging differs depending on the type of affected organ (Table 1).
2. *Specific criteria related to T categories*:
   The extent of the primary tumour is defined by T category. Its description differs depending on the site and the organ of origin. Table 2 shows the specific criteria for T categories.
3. *Specific criteria related to N categories*:
   Rouviere introduced the concept of a first echelon/ station (the first set of lymph nodes receiving the direct drainage of a specific organ) and second echelon/station (the nodes which receive lymph drainage from another lymph node rather than directly; which includes prograde and retrograde drainage) of lymph nodes. He rejected 'the concept of a regional node bearing area.' Table 3 shows the specific criteria for N categories.
4. *Specific criteria related to M categories*:
   The distant metastasis category (M category) specifies whether distant metastasis is present, its location, and burden. Presence of metastasis reflects poor prognosis, and cure is rare. Metastases usually affect the anatomical sites along the venous drainage of the primary organ.
   E.g., Head and neck cancers spread along its venous drainage to the right side of the heart and then to the lung; gastrointestinal cancers drain to the portal vein and then to the liver; prostate cancer spreads via Batson paravertebral venous plexus to the spine.
   M0: No evidence of metastasis
   M1: Solitary metastasis in a single organ without functional impairment
   M2: Multiple metastases to a single organ with minimal functional impairment
   M3: Multiple metastases to multiple organs with minimal to moderate functional impairment
   M4: Multiple metastases to multiple organs with moderate to severe functional impairment

Table 1 Difference between hallow organ and solid organs [2, 3]

Characteristics	Hollow organs	Solid organs
Function	Propel a bolus, vital secretions, undesirable waste products passageway through a system	Glandular function type exocrine glands
Histological architecture	Saccular/tubular organ	Uniform parenchyma with capsule
Anatomic—physiologic units	Multilayered walls and in series	Parallel arrangement and divided into lobes
Capillary network	Avascular mucosa resting on a soft stromal bed rich in lymphatics and capillaries	Intimately related structurally to cellular function
Pair	Concentrically arranged, outer border is a thin layer of mesothelial cells such as the serosa, adventitia, or peritoneum	Paired/bilobed
Surrounding structures	Similar and in-continuity, have sphincters	Separate and different histogenesis
Metastatic spread	Lymphatics and regional nodes	Haematogenous

2.2 Groome's Criteria and the Staging System [4–6]

The T, N, and M system individually creates too many small groups that make a staging system practically tricky. To circumvent this, tumours are grouped into four major stage groups for ease of comparison. However, stage groups are still very heterogeneous. To solve this, the new TNM staging has followed the modified Groome's criteria while incorporating evidence-based non-anatomic factors. The modified Groome's criteria are as follows:

1. Hazard consistency: To gauge the similarity of overall survival (OS) rates for subgroups defined by T, N, and M within each stage group scheme.
2. Hazard discrimination: To assess the differences in OS between stage groups to measure how equally they were spaced. The survival rate associated with a particular group should be significantly different from the one above or below.
3. Explained variance: To estimate the percentage of OS variation defined by the stage grouping. The assigned

Table 2 Special criteria for T category [2, 3, 11]

Specific criteria		T1	T2	T3	T4
Size: The largest dimension size consideration for few organs only (0.5–1.0 cm consist of 10^6 cells and relate to age of the tumour)	Organ				
	Oral cavity, Pancreas, Oropharynx p16 negative	≤2 cm	2–4 cm	>4 cm	More invasive Unresectable in few cancers
	Anal canal, Liver, breast	≤2 cm	2–5 cm	>5 cm	Invades adjacent structures
	Lung	≤3 cm	3–5 cm	5–7 cm	>7 cm, invades adjacent tissues
	Soft tissue tumors—Retroperitoneum	≤5 cm	5–10 cm	10–15 cm	>15 cm
	GIST[a]	≤2 cm	2–5 cm	5–10 cm	>10 cm
	Kidney	≤7 cm	7–10 cm	>10 cm and invasion	Invasion of adjacent structures
Depth of invasion					
(a) Solid organs	Localised		Infiltrate capsule or fibrous layer, ligaments	Infiltrate bone, cartilage, skin	Infiltrate viscera, major nerves, arteries, veins, destruction of bone
(b) Hollow organs	Infiltrates submucosa		Infiltrate muscularis (intrinsic muscles)	Infiltrate extrinsic muscle and serosa	Infiltrate viscera
Mobility	Mobile		Restricted mobility	Fixed	Fixed and destructive
Neighboring structures	Does not infiltrate adjacent or surround structures (superficial)		Extension to Adjacent structures [[b]Attached structures] (deep invasion)	Extension to Surrounding structures ([c]detached structure)	Viscera, causing fistula or sinus (massive destruction)
Surface spread (a) Hollow organ (circumferential involvement)	<1/3 Circumference		1/3 to 1/2 Circumference	1/2 to 2/3 Circumference	>2/3 Circumference
(b) Visceral regions (R)	<½ visceral region (R1)		>1/2 visceral region (R1)	>1 visceral region (R1 + R2)	>2 visceral regions (R1 + R2 + R3)

[a] *GIST* gastrointestinal stromal tumour

[b] Attached structures: Ill-defined boundary between site of origin and these structures. It has similar tissue type and function.

[c] Detached structures: It is separate, but juxtaposed to the site of tumour origin. It has different tissue type and function.

stage should give a good approximation of survival for the individual. It should have high cure/outcome predictive ability.

4. Equitable distribution: The distribution of patients (sample size) is balanced among the groups. To scrutinise the difference in sample sizes across stage groups. Thereby, it maximises statistical power in each group.
5. Likelihood difference: To weigh the difference in the goodness of fit between the models. This is used to assess the various models proposed for staging.

2.2.1 Stage Migration

Hazard discrimination is lost when new prognostic factors or change in technology is applied. This happens due to stage migration. Stage migration leads to a curious statistical phenomenon called ‘the Will Rogers phenomenon’ [7]. This happens due to the shift of the subset of patients with relatively worser outcomes within the previously assigned ‘good’ stage to a higher ‘bad’ stage with poorer outcomes than the previous stage. This improves the survival rate in both groups without any change in individual outcomes. This can be solved with better attention to sound scientific research and clinical taxonomy.

Therefore, it is essential to adopt the staging system, which fulfils all criteria as mentioned earlier.

2.3 General Rules of the TNM System [8, 9]

2.3.1 Staging Groups

Following are the five staging groups:

1. Clinical staging (cTNM): It is used before any treatment. It includes the clinical history, examination, lab tests, biopsy, radiographic, and endoscopic procedures. Surgical exploration without resection is also used to assign the cTNM staging. Whenever there is a doubt regarding the T, N, or M category, the lower category is used. All diagnosis should be confirmed histologically, even for cTNM staging.

Table 3 Special criteria for N category [2, 3]

Specific criteria	N0 Node negative	N1 First station (sentinel)	N2 First station	N3/N3a First station	N4/N3b,3c Second station (juxta regional)
Drainage					
(a) Ipsilateral	–	√Ipsilateral	√Ipsilateral	√Ipsilateral	–
(b) Bilateral/ contralateral	–	√Ipsilateral	√Bilateral or √Contralateral	√Ipsilateral or √Contralateral	√Contralateral
(c) Distant	–	–	–	–	√Distant
Shape	Discoid/ flat	Round	Round	Round, matted	Round
Consistency	Soft to firm	Firm to hard	Firm to hard	Firm to hard	Firm to hard
Size	≤2 cm	2–3 cm	>3 cm and ≤5 cm	>5 cm	>10 cm
Number	–	Solitary	2–3	≥4 and <10	>10 and ≤16
Mobility	Mobile	Mobile (no capsular invasion)	Partial matted (microscopic capsule invasion) muscle (fascia) invasion	Fixed to vessels, bone, large blood vessels, skin (DLI), nerves (PNI)	Fixed and extensive nodal necrosis leading to destruction of bone and skin
Presence of lymph node is assigned as Stage III (or its subdivisions)	Except for few sites, they are down staged and assigned stage I. e.g., DTC <55 years, p16 positive oropharyngeal carcinoma, cervical uterus and stomach cancer. Assigned stage II. e.g., DTC >55 years, nasopharynx, pleural mesothelioma, testis, oesophagus, distal extrahepatic bile duct, exocrine pancreas, lung and breast cancers.				
	Presence of node may be upstaged to Stage IV for mucosal melanoma, liver, thymus, anaplastic thyroid cancer, GIST, renal pelvis, ureter, uveal melanoma, prostate, bone tumours, soft tissue, trunk and of extremities sarcoma.				

DLI dermal lymphatic invasion, *PNI* perineural invasion

2. Pathologic staging (pTNM): It is used if surgery is the first definite therapy. Pathological review of the resected surgical specimen, operative findings, and diagnostic workup from clinical staging are combined for pTNM. It provides essential pathological parameters, which prognosticate and guide subsequent therapy and outcomes.
3. Post therapy or post neoadjuvant therapy (Treatment-related, yTNM): It is used if radiation and/or systemic therapy is given as definitive or neoadjuvant treatment (NADT) before surgery. However, a short course of endocrine therapy in breast cancer or prostate cancer does not meet the criteria for NADT.
    (a) ycTNM: Post NADT (radiation or systemic therapy)—clinical and imaging.
    (b) ypTNM: Post NADT (radiation or systemic therapy and followed by surgery)—pathological.

   The response to NADT is recorded as complete/partial and no response, or by a scoring system or regression score. Presence of non-necrotic viable tumour is required for confirmation of residual tumour. Necrosis, mucin pools, and other reactive and degenerative changes do not confirm the viable tumour and are not considered for residual cancer. Mucin pools and necrotic cells have no role in ypT and ypN.
4. Recurrence or retreatment (rTNM) is used at recurrence after a disease-free interval or progression without a disease-free interval.
    (a) rcTNM: Clinical recurrence staging with/without imaging and biopsy.
    (b) rpTNM: Pathological staging of recurrence. This does not replace clinical (c), previous pathological (p), and/or post-therapy (y) staging.
5. Autopsy (aTNM)—It is used when cancer is discovered incidentally at autopsy. This does not apply to the previously diagnosed cancer patient who has undergone an autopsy.

2.3.2 The TNM Clinical Classification

1. *T category: Primary tumour: Clinical*

cTx: information regarding T category of the primary tumour is not available, or it is not known, or primary tumour cannot be assessed.

cT0: No evidence of a primary tumour.

cTis: Carcinoma in situ.

cT1–4: Increasing size and/or extent of the primary tumour. Based on physical examination, imaging, endoscopy, biopsy, and surgical exploration without resection.

2. *N category: Regional lymph nodes: Clinical*

cNx: No information about the N category or it is unknown or cannot be assessed.

cN0: No regional lymph node involvement.

cN1–3: Increasing involvement of regional lymph nodes.

It may be further divided and subdivided for specific cancers. e.g., Breast, colon, head and neck cancer.

cENE: If a gross extranodal extension is evident on clinical examination.

3. *M category: Distant metastasis: Clinical*

cM0: There are no symptoms/signs of distant metastasis. History and physical examination and/or imaging may be used to assign the cM0 category.

cM1: Clinical/imaging/exploratory surgery or endoscopy are suggestive of distant metastasis without microscopic evidence.

There is no Mx designation. Clinically considered M0 if no proof of metastasis on clinical history or physical findings or imaging. Patient with a negative biopsy of a suspected metastatic site is classified as cM0. Direct extension from the primary tumour or lymph nodes into a contiguous or adjacent organ is not included in the M category.

According to the location (organ) of distant metastasis, M1 category may be specified further with following notations:

M1 PUL: Pulmonary Metastasis
M1 HEP: Hepatic Metastasis
M1 OSS: Osseous Metastasis
M1 SKI: Distant Skin Metastasis
M1 BRA: Brain Metastasis
M1 MAR: Bone Marrow Metastasis
M1 ADR: Adrenal Metastasis
M1 PLE: Pleura Metastasis
M1 PER: Peritoneum Metastasis
M1 LYM: Distant Lymph Nodes Metastasis
M1 OTH: Other

cM0(i+): Circulating tumour cells (CTCs) in blood or Disseminated tumour cells (DTCs) in organs and micrometastasis in the bone marrow are detected by RT-PCR, IHC or cM0(mol+) molecular techniques.

Presence of distant metastasis is assigned as advanced stage IV (A/B/C) except for differentiated thyroid cancer <55 years (Stage II), testis and Gestational trophoblastic neoplasms (Stage III).

2.3.3 The TNM Pathological Classification

1. ***pT: Primary Tumour: Pathological***
   (a) pTx: Histologically, primary tumour cannot be assessed

   pT0: No histological evidence of primary tumour
   pTis: Carcinoma in situ
   pT1–4: Histologically increasing size and/or local extent of primary tumour

   Size is measured in mm and rounded for the nearest whole millimetre

   (b) **Unresectable tumour:**

   pT category is assigned without tumour resection after biopsy confirmation from the primary tumour or microscopic confirmation of the highest pN.

   (c) **Grade**: It is a qualitative assessment of the degree of differentiation, which provides information regarding the risk of metastasis and prognosis. If more than one grade of differentiation is present, then the highest grade is recorded.

   Grade X: Grade of differentiation cannot be assessed
   Grade 1: Well-differentiated
   Grade 2: Moderately differentiated
   Grade 3: Poorly differentiated
   Grade 4: Undifferentiated

   Sometimes Grade 3 may be combined with poorly differentiated and/or undifferentiated, e.g., Esophagus and stomach.

   For thymus and Merkel cell carcinoma, there is no recommended histologic grading system. There are unique grading systems for tumours of specific organs, e.g., breast, prostate, and liver.

   (d) **Lymphovascular invasion (LVI)**:

   LVI Coding:
   0: LVI not present/not identified
   1: LVI present/identified
   2: (L) Lymphatic and small vessel invasion only
   3: (V) Venous (large vessel) invasion only
   4: Both lymphatic and small vessel and venous (large vessel) invasion
   9: Presence of LVI unknown/indeterminate

   Intratumoral or extratumoral; focal or multifocal also noted.

   (e) **Perineural invasion (PNI)**:

   PnX: Perineural invasion cannot be assessed
   Pn0: No perineural invasion
   Pn1: Perineural invasion present

   Intratumoral or extratumoral; focal or multifocal also noted.

2. ***pN: Regional Lymph Nodes: Pathological***
   (a) pNx: Histologically, regional lymph nodes cannot be assessed
   (b) pN0: Histologically, no regional lymph node metastasis

   pN1–3: Histologically, increasing involvement of regional lymph nodes

   The number of lymph nodes removed is documented to provide optimal prognostic information. Even though fewer than the recommended number of nodes are resected, it is categorised as pN0.

   Apart from the number of lymph nodes removed, its location, size of the node, and the node's largest metastatic deposit are also documented.

(c) **Macrometastasis:**

Tumour deposit >2 mm. It is considered pN1.

(d) **Extranodal extension (ENE/ECE/ECS):**

Extension of metastasis through the lymph node capsule into adjacent tissues are documented.

$pENE_n$: None

$pENE_{mi}$: microscopic ENE $\leq$ 2 mm

$pENE_{ma}$: Major ENE >2 mm or gross ENE. Both qualify as pENE (+)

If the tumour directly extends to the lymph node, it is classified as node-positive. Rounded tumour nodules in regional areas are considered nodes that are completely replaced by tumour and are not part of T category.

3. ***pM: Distant Metastasis: Pathological***

pM1: Distant metastasis microscopically confirmed

There is no designation of pM0. Direct extension from the primary tumour or lymph nodes into a contiguous or adjacent organ is not included in the M category.

Metastasis to both sides of a paired organ is considered a single metastatic site.

e.g., Bilateral lung metastasis is considered as one distant site as lung.

If confirmed microscopic evidence of distant metastasis is available, pM1 is used for clinical and pathological stage IV.

e.g., cT3 cN1 pM1, c Stage IV and cT3 cN1 pM1, p Stage IV.

2.3.4 Additional Descriptions

1. **Multiple Tumours**:

Multiple tumours may occur in the same organ at around the same time (synchronous) or at separate points in time (metachronous).

Synchronous primary tumour:

(a) Cancers occurring in the same organ system (or paired organs) with diagnosis date ≤4 months apart. It also includes disease diagnosed at the time of surgery for first cancer, if surgery is the planned first course of therapy.

(b) They have the same histology and occur in one organ. 'm' suffix is used for multiple synchronous 'invasive' primary tumors in a single organ. The tumour with the highest T category is highlighted, e.g. pT3(m) N0M0 or another alternative is to write the number of tumours, e.g. pT2(3) N0M0.

(c) Synchronous primary tumours in paired organs are staged separately, e.g., lung, kidney and breast. However, for thyroid, liver and ovarian tumours, multiplicity is incorporated in T category and, therefore, not staged separately. It does not apply to multiple foci of in situ cancer or mixed invasive and in-situ cancer.

Metachronous primary tumours:

(a) Cancers occurring in the same organ system with diagnosis date are more than 4 months apart. It does not include disease identified during the surgery for the first cancer, if surgery is the planned first course of treatment and is conducted >4 months after the first diagnosis.

(b) Metachronous primary (occurring in the same organ or different organs) are staged independently as new cancer.

2. **Unknown Primary**:

An unknown primary site is assigned T0 if there is evidence of nodal and/or distant spread and a primary source is suspected, but not identified by clinical examination, imaging or histology. T0 is designated when an expected primary site refuses to show any evidence of malignancy. When a primary site cannot be determined by histology, like poorly differentiated carcinoma, it is not categorised as T0, but is just designated as unknown primary.

(a) cT0: If physical examination, imaging, endoscopy and other diagnostic procedures do not identify a primary tumour.

(b) pT0: If after surgical resection of a suspected primary tumour, it does not show the tumour and is not confirmed on biopsy.

(c) T0 Category: In the absence of any evidence or unknown primary, the staging is done according to the clinically suspected anatomic site.

e.g., Metastatic adenocarcinoma in axillary lymph nodes, suspected from breast, T0N1M0, Stage II.

(d) For head and neck sites, T0 category is not used, except for HPV-associated oropharyngeal, EBV-associated nasopharyngeal cancers and major salivary gland cancers.

This is different from T_X. 'T_X' designation is given when the information about a former primary is not available, or the clinical scenario is such that the primary cannot be assessed. 'T_X' category use should be minimised.

3. **Sentinel Lymph Node**:

cN1(sn): If SLN biopsy is done for diagnostic workup, then the positive node is denoted as cN1(sn).

pN1(sn): If SLN biopsy is done as a part of initial surgical management, then the positive node is represented as pN1(sn).

If the patient has undergone a completion lymph node dissection following SLN biopsy, then the suffix is not used. pN1 is used.

pN0 (sn): Negative nodes after sentinel node biopsy.

pN0 (i+) (sn): Isolated tumour cells <0.2 mm in sentinel node biopsy sample.

4. **FNA/Core Biopsy:**

cN1(f): If FNA/Core biopsy is done on lymph nodes as a part of the diagnostic workup, then cN1(f).

pN1(f): If FNA/Core biopsy is done as a part of primary site surgical resection with no lymph node dissection performed, then the positive node is denoted as pN1(f).

If a completion lymph node dissection is done as part of the initial surgery, it is pN1.

5. **Isolated Tumour Cells (ITCs) (i+)**:

   Single tumour cell or small clusters of cells ≤0.2 mm.

   A cluster of <200 cells in a single histological cross-section.

   They do not show proliferation, stromal reaction, or penetration of vascular or lymphatic sinus walls. As they represent in-transit disease and not something that stations and proliferates, their presence in nodes is not usually considered positive except for few aggressive tumours. Therefore, they are categorised as N0 in lymph nodes and M0 in distant sites.

   e.g., Breast and gynecologic cancers; cN0(i+) if detected on diagnostic workup or pN0 (i+) on IHC as a part of surgical management.

   pN0 (mol+) if no tumour cells histologically, however positive by molecular (RT-PCR) findings/ flow cytometry.

   However, in melanoma and Merkel cell carcinoma, they are considered positive. pN1(i+).
6. **Micrometastasis:**

   Tumor deposit >0.2 mm to ≤2.0 mm. cN1 (mi) if detected on diagnostic workup or pN1 (mi) for single node and pN2b (mi) or pN2c (mi) for multiple nodes as a part of surgical management.
7. **Residual Tumour and Surgical Margins:**

   'R' represents the absence or presence of residual cancer after treatment.

   However, the R designation is not incorporated into TNM staging itself, recorded in medical record and cancer registry as essential information for subsequent treatment and prognostication.

   The R categories for the primary site following surgical manoeuvres:

   Rx: Presence of residual tumour cannot be assessed
   R0: No residual tumour
   R1: Microscopic residual tumour
   R2: Macroscopic residual tumour at the primary cancer site/regional nodal sites (does not apply to metastatic disease, which is not resected at surgical exploration)

   After tumour resection, margin status is noted either as negative, microscopic positive, macroscopic positive, or could not be assessed. Presence of disease at the margin of resection indicates the risk of recurrent cancer and more advanced T or N tumour.
8. **Paediatric Tumors:**

   There is no classification of paediatric tumours incorporated in the TNM system. This is because of the lack of an international standard staging system for many paediatric tumours. A recommendation was published in 2014 on paediatric staging to facilitate the collection of the stage by population-based cancer registries.

2.3.5 Stage Grouping [8–10]

Each patient can be placed in 125 different categories, which may be inconvenient for the clinician. Cancer progresses in an orderly, predictable fashion in most cases, though seldom not. The Venn diagram of cancer spread is used to illustrate disease progression and patients with similar prognosis are grouped by using prognostic stage group tables. Thus, the stages are divided into four and denoted by Roman numerals (I–IV).

The unified stage grouping helps to compare patterns of spread rationally. In case of doubt regarding the stage grouping, the lower group is assigned.

Staging Rules

Figures 1, 2, 3, 4, and 5 shows the five rules of staging adopted for the TNM staging.

1. Stage 0:

Stage 0 includes in-situ and non-invasive cancers.

Term 'non-invasive' usually denotes that the disease has not crossed the basement membrane. 'In-situ' means it has not crossed the boundary to attain spreading potential. That boundary could be basement membrane in some cancers like oral cavity or muscularis mucosae in the colon. Generally, it is considered to have no potential for regional or distant spread. So, lymph node assessment is not necessary to assign final pathologic stage 0 for in-situ neoplasia.

   (a) cTis N0 M0, (clinical stage 0is): In situ neoplasia identified during diagnostic workup.

   (b) The category non-invasive (Ta) is only defined in a few cancers (e.g., urinary bladder).

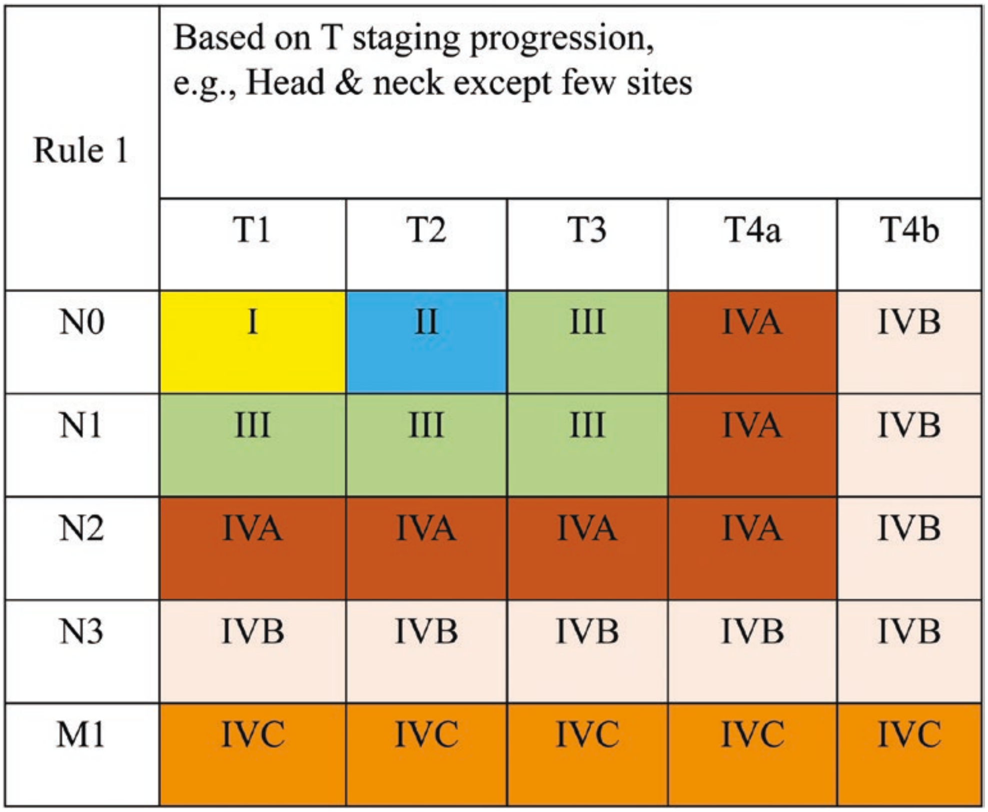
   cTaN0M0, (clinical stage 0a): Non-invasive papillary carcinoma identified during diagnostic workup.

   (c) Rarely pathology may not be able to identify the invasive component and is reported as Tis with regional nodal involvement. In that case, the appropriate stage group may be assigned as per the N category by the physician. However, in the cancer registry, the stage group is not assigned.

   e.g., In breast, ductal carcinoma in situ with nodal metastasis may represent nodal metastasis from an unidentified invasive occult primary cancer.

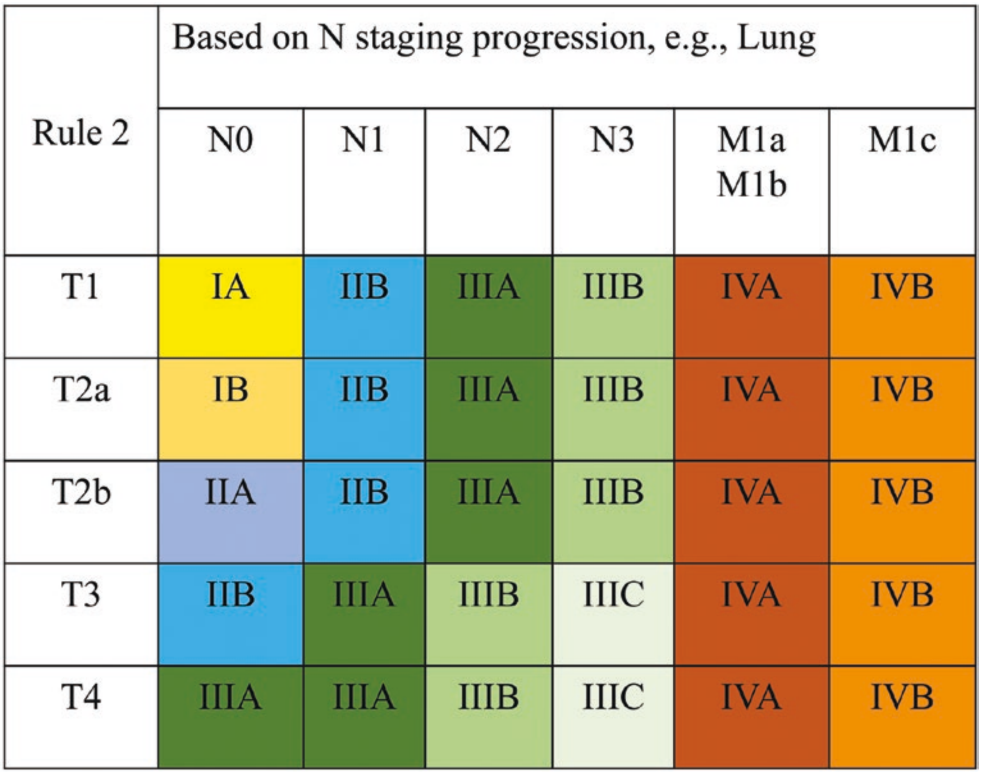
   In melanoma, melanoma in situ with nodal metastasis: It may represent the biologically regressed primary tumour.

2. If a complete pathological response has occurred, then ypTNM is ypT0N0M0; no stage group is assigned and not classified as Stage 0 because that would denote in situ neoplasia.



Rule 1	Based on T staging progression, e.g., Head & neck except few sites				
	T1	T2	T3	T4a	T4b
N0	I	II	III	IVA	IVB
N1	III	III	III	IVA	IVB
N2	IVA	IVA	IVA	IVA	IVB
N3	IVB	IVB	IVB	IVB	IVB
M1	IVC	IVC	IVC	IVC	IVC

Fig. 1 Rule 1 of the TNM staging [9–11]



Rule 2	Based on N staging progression, e.g., Lung					
	N0	N1	N2	N3	M1a M1b	M1c
T1	IA	IIB	IIIA	IIIB	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVB

Fig. 2 Rule 2 of the TNM staging

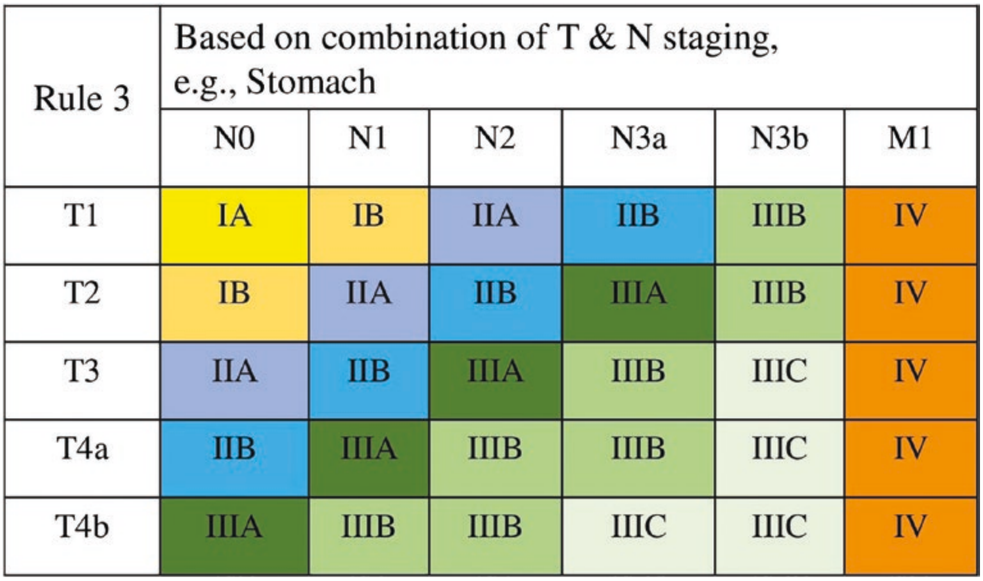


Fig. 3 Rule 3 of the TNM staging

Rule 3	Based on combination of T & N staging, e.g., Stomach					
	N0	N1	N2	N3a	N3b	M1
T1	IA	IB	IIA	IIB	IIIB	IV
T2	IB	IIA	IIB	IIIA	IIIB	IV
T3	IIA	IIB	IIIA	IIIB	IIIC	IV
T4a	IIB	IIIA	IIIB	IIIB	IIIC	IV
T4b	IIIA	IIIB	IIIB	IIIC	IIIC	IV

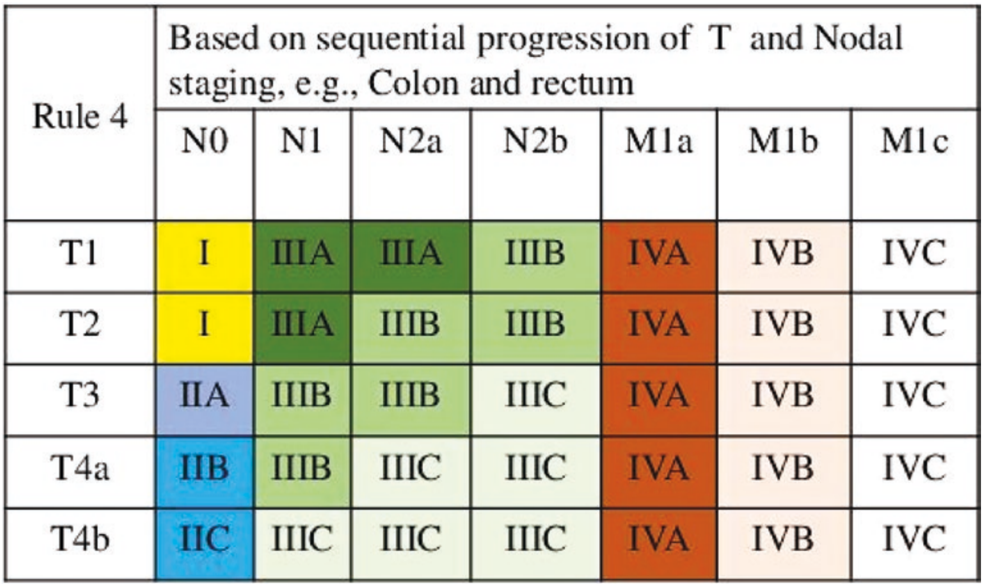


Fig. 4 Rule 4 of the TNM staging

Rule 4	Based on sequential progression of T and Nodal staging, e.g., Colon and rectum						
	N0	N1	N2a	N2b	M1a	M1b	M1c
T1	I	IIIA	IIIA	IIIB	IVA	IVB	IVC
T2	I	IIIA	IIIB	IIIB	IVA	IVB	IVC
T3	IIA	IIIB	IIIB	IIIC	IVA	IVB	IVC
T4a	IIB	IIIB	IIIC	IIIC	IVA	IVB	IVC
T4b	IIC	IIIC	IIIC	IIIC	IVA	IVB	IVC

3. Stage IV: Stage assigned is stage IV if evidence of distant metastasis, even if T or N category is unknown.

2.4 Cancer Staging Systems in Clinical Practice [8, 9, 11]

2.4.1 Supplementary/Alternate Staging/Grading System to TNM System: Few Examples

1. Breast cancer: Scarff-Bloom-Richardson (SBR) (Nottingham) grading system.
2. Prostate Cancer: The Gleason scoring system and the grade grouping (1–5).
3. Hepatocellular cancer: Barcelona clinic liver cancer (BCLC) staging, Hongkong liver cancer (HKLC) staging.
4. Perihilar bile duct: Bismuth-Corlette classification.
5. Gynaecologic cancers: Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging.
6. Thyroid cancers: The MACIS prognostic scoring systems, American Thyroid Association (ATA) risk stratification system.
7. Soft tissue sarcoma: The French Federation of Cancer Centers Sarcoma Group (FNCLCC) histologic grading system.
8. Colorectal cancer: Dukes staging system (A–C), Modified Astler-Coller classification (MAC) (A–D).

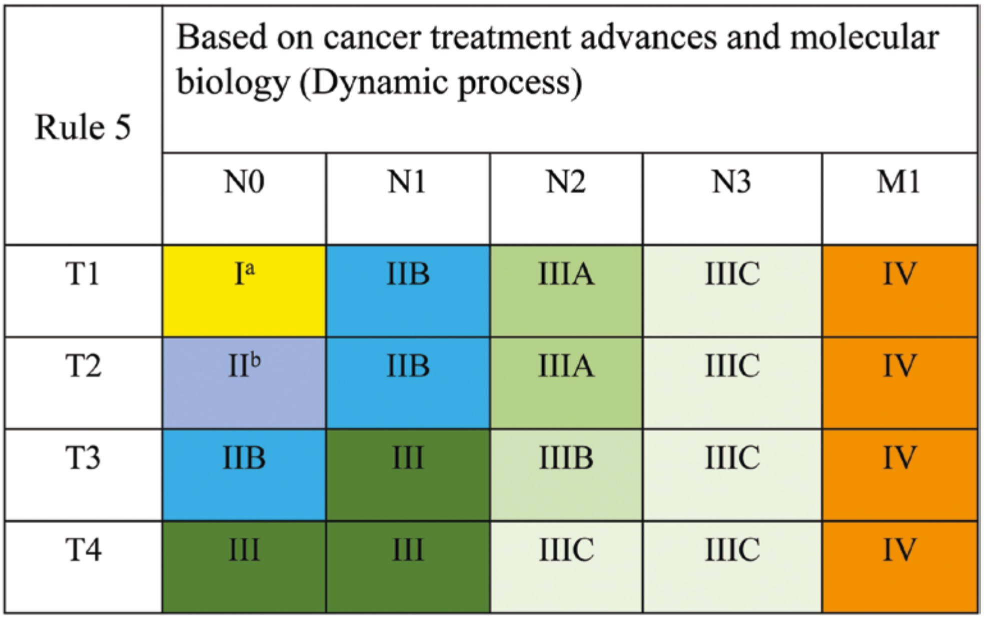


Fig. 5 Rule 5 of the TNM staging

Rule 5	Based on cancer treatment advances and molecular biology (Dynamic process)				
	N0	N1	N2	N3	M1
T1	I[a]	IIB	IIIA	IIIC	IV
T2	II[b]	IIB	IIIA	IIIC	IV
T3	IIB	III	IIIB	IIIC	IV
T4	III	III	IIIC	IIIC	IV

2.4.2 Publications and Organisations Associated with TNM System [1, 8]

Publications

1. World Health Organization (WHO) Classification of Tumours, pathology and genetics, 2000–2016.
2. WHO International Classification of Diseases for Oncology (ICD-O), 2000.
3. American College of Radiology (ACR) Appropriateness Criteria.
4. CAP Cancer protocols.
5. National Comprehensive Cancer Network Clinical Practice (NCCN) Guidelines in Oncology.
6. American Society of Clinical Oncology (ASCO) Guidelines.

Organisations

1. Centers for Disease Control and Prevention, USA (CDC).
2. International Federation of Gynaecology and Obstetrics (FIGO).
3. International Association of Cancer Registries (IACR).
4. International Agency for Research on Cancer (IARC).
5. International Association for the Study of Lung Cancer (IASLC).
6. International Collaboration on Cancer Reporting (ICCR).

2.4.3 The AJCC-UICC Lexicon Project [8]

In January 2012, the UICC and AJCC initiated a comprehensive analysis of staging nomenclature, viz. the AJCC-UICC Lexicon Project.

The staging terminologies should be categorised into four main groups:

1. Anatomic stage: Disease extent and timing/classification, also tumour markers reflect tumour burden. (e.g. serum PSA in prostate cancer).
2. Tumour profile: Morphology, pathological grade, growth pattern, tumour markers, the steroid receptive status (estrogen receptor/progesterone receptor), DNA content (ploidy and S-phase), proliferative indices, viral load molecular and genetic markers. These are predictive, prognostic, and companion diagnostic markers.
3. Patient profile: Age, race, gender, level of education, socioeconomic status, performance status, comorbidity—coronary artery disease, obesity, hypertension, diabetes mellitus, immunodeficiency.
4. Environment: Treatment-related, its availability, education (expertise, access, ageism, healthcare delivery), socioeconomic status, quality of imaging, and quality of management.

2.5 Evolution of Staging System and Their Implications

1. **History of Staging System** [1, 8, 9]

   Cancer of the cervix was first staged in the 1920s. In 1929, the League of Nations Health Organization led the work on 'clinical classification of cancer.' The French surgeon, Pierre Denoix, proposed the 'Tumour—node—metastasis (TNM) system' between 1943 and 1952 based on cancer's anatomic extent. In 1950, the UICC appointed a committee on Tumour Nomenclature and statistics. It launched ‘Uniform technique for a Clinical Classification by the TNM classification’ along with the International Commission on Results of the treatment of cancer (ICPR) in 1953. The Research Commission of the UICC had configured a special committee on clinical stage classification and applied statistics in 1954. The clinical staging for breast and larynx was published in 1958 and revised proposals for breast cancer in 1959. The American Joint Committee for Cancer Staging and End Results Reporting (AJCC) was founded on January 9, 1959. Cancer of head and neck, alimentary tract, breast, urological sites, and skin were staged between 1960 and 1967 (Nine brochures for 23 body site classification proposals). UICC published ‘livre de Poche’ (the first collective TNM handbook) in 1968. In 1980, AJC was renamed to the American Joint Committee on Cancer (AJCC). The UICC and AJCC and collaborated in 1978 and resulted in the simultaneous publication of the staging manual. In 1987, the UICC and the AJCC TNM classification was unified.

2. **Evolution and Its Implication**

   Evolving for over 50 years, the current 8th edition includes 15 organ systems and 130 primary sites (Table 4) [9, 11]. It reflects all the assimilated evidence-based knowledge regarding cancer biology, etiology, prognostic factors, statistical methodology, and recent advances in the field.

Table 4 Evolution of TNM system [1, 8, 10]

Edition UICC 1950	Edition AJCC 1959	TNM Organ system	TNM Primary sites/ disease
1st (1969) Expansion	–	7	27
2nd (1974)	–	8	30
3rd (1978) Checklist	1st (1977)	9	33
3rd (1982) Illustration—Atlas	2nd (1983)	10	36
4th (1987) Unification	3rd (1988)	12	45
4th (1993) Refinement—Supplement	4th (1992)	12	56
5th (1997) Prognostic factors—Monograph	5th (1997) (Adopted staging from other oncology cooperative investigative groups)	11	55
6th (2002) TNM Mobile Edition 2001/02; TNM Online 2003	6th (2002)	11	56
7th (2009)	7th (2009)	11	71
8th (2016)	8th (2016)	15	130

2.5.1 Concerns Associated with the Revisions in Staging System

(a) Newer changes incorporated in the staging system may disturb the staging consistency concerning previously acquired data. Therefore, the anatomical basis is maintained. It maintains consistency with the past versions of staging.

(b) A revised staging system may diminish the comparability of the data over time. Therefore, in general, the TNM revision happens every 5–7 years. This gives sufficient time for implementing the staging system in clinical practice and allows comparisons across historical and contemporary eras.

(c) Too many changes make the staging system more complex to use and practice. Therefore, only clinically essential and relevant changes are incorporated to have broader applicability. They are selected based on available methods of assessment and depending on the need for patient management.

(d) Newer prognostic factors may not apply to low resource countries. Therefore, the anatomic extent as a backbone of the staging system is maintained. It is still applicable to the patient population for whom new prognostic factors are not available due to cost, lack of expertise, logistic issues, or reporting systems.

(e) Tumours with higher histological grade are more aggressive clinically than those with low-grade. However, the cancer staging system seldom relies on the grading system, it is based on the extent of primary tumour and spread to regional lymph nodes or distant metastasis. Incorporation of the tumour grading into the staging system can show a strong survival association, e.g., colorectal cancer.

(f) The TNM staging system is useful as a classification system at a population level. Its utility for the individual patient has been questioned. The 8th TNM cancer staging manual has attempted to address this issue by incorporating molecular markers to supplement the traditional approach.

2.5.2 Types of Changes in the TNM System [10]

(a) Minor 1+: Same TN designation but definition change, e.g. head and neck, penis

(b) Moderate 2+: Designation change T or N, but not stage, e.g. thyroid, breast

(c) Major 3+: Major change T or N, with new criteria and new substage, e.g., nasopharynx, adenocarcinoma thorax

(d) Marked 4+: New T and N criteria definition and shift in stage, e.g. thoracic oesophagus, prostate

(e) New 5+: New TNM staging system, e.g. mucosal melanoma, small intestine adenocarcinoma, adrenal gland

2.6 Prognostic Factors and 'Grid' [9, 12, 13]

Prognostic factors (PF) may explain the heterogeneity associated with a disease's expected course and outcome.

Levels of prognostic factors:

(a) Level I PF: It is statistically significant
(b) Level II PF: It is an independent PF
(c) Level III PF: It is of clinical relevance

2.6.1 Grids of Prognostic Factors

UICC Manual of clinical oncology, 9th edition has proposed the framework for classification of prognostic factors with 'the Grids of prognostic factors' for various cancer sites. It includes a 'subject-based' classification (tumour related, host-related, and environmental-related) and 'clinical relevance-based' classification (essential, additional and new and promising prognostic factors). The grids are reproduced in the 8th edition of UICC TNM classification. Table 5 shows the grid classification and a few examples.

2.7 Changes Observed in the TNM System

2.7.1 C-Factor [8, 9]

The Certainty Factor (C factor) denotes the classification's validity as per the diagnostic method used. The C Factor has been removed in the eighth edition of the Staging system.

Table 6 shows cancer site specific revisions in TNM staging.

2.8 Future of Cancer Staging [3, 14]

The TNM staging is mainly a surgical system built on anatomic parameters. It's a temporal determinism that is based on the contiguous spread of disease. Nomograms and artificial neural networks should be utilised in the future to integrate various relevant prognostic factors. The following elements may be incorporated into the TNM system:

1. Tumour-related: histologic features (especially grade and cell type), location, gross appearance, multiplicity, dimension of margin, ease of resectability, tumour marker levels, hormone receptors positivity, somatic mutations and molecular signature of tumour cells.

Table 5 UICC prognostic factors 'grid' with few examples [9, 12]

		Subject-based classification		
Prognostic factor		***Tumor related*** Anatomic extent Pathological parameters Tumor biology and markers Symptoms related	***Host related*** Host demographics Acquired host factors	***Environmental related*** Interrelationship of Treatment, Quality and Education with Physician, Health care system and Society
Essential **Fundamentally required for decision making**	**Clinical Relevance-Based Classification**	Gleason sum score (Prostate) T, N and M category (Anal canal) Circumferential margins (Rectum) Extracapsular extension (Oral cavity)	Age >70 (Larynx) Menopausal status (Breast) Performance status (Cervix) Germline mutation RBI allele (Retinoblastoma)	Residual disease after resection (Bone) Cigarette smoking (Anal canal) Screening programme (Colon and rectum) Quality of and availability of anticancer therapies (Cervix)
Additional **Not absolutely required for decision making** Finer prognostication No impact on the treatment Stratification of patient		Tumor volume (Larynx) Hypoxia (Oral cavity) CA 19.9 level (Pancreas) CA 125 (Ovary)	Comorbidity (Oropharynx) BRCA 1 or 2 (Breast) LDH (Nasopharynx) Hepatitis activity (Liver)	Nutritional support (Oesophagus) Extent of resection (Stomach) Management by a multidisciplinary sarcoma team (Bone) Centre volume and experience (Colon and rectum)
New and promising **Not enough evidence for use** New factors Prognostication Based on cancer biology		EGFR receptor (Oropharynx) Ki67 (Breast) Molecular profile (Thyroid) FGFR2 mutations (Biliary tract and gall bladder)	Serum MyoDI (Cervix) IL10 and VEGF (Liver) HSV virus (Anal canal) Race: Asian or non-Asian (stomach)	In utero detection of Rb (Retinoblastoma) Immunotherapy (Melanoma) Pathological response to neoadjuvant therapy (Pancreas) Neutron vs. photon radiotherapy (Major salivary glands)

Table 6 Cancer site-specific revisions in TNM staging [9, 11]

Sites	Major changes/revision done in TNM staging
New chapter and/or new TNM staging added	**7th Ed.** Mucosal melanoma of the head and neck, gastrointestinal stromal tumours (GIST), neuroendocrine tumours, Merkel cell carcinoma, appendix, adrenal gland, ocular adnexal lymphoma **8th Ed**. HPV-mediated (p16+) oropharyngeal cancer, cutaneous squamous cell carcinoma of the head and neck, cervical lymph nodes and unknown primary tumours of the head and neck, thymus, parathyroid Soft tissue sarcoma: New staging: head and neck, retroperitoneal, trunk and extremities, thoracic and abdominal viscera, unusual histologies and sites New TNM staging: Pelvis and spine bone sarcomas
Separate/major revisions	**7th Ed.** Intrahepatic bile ducts, perihilar bile ducts, distal bile duct **8th Ed.** Oropharynx (p16-) and hypopharynx, nasopharynx, medullary thyroid cancer, exocrine pancreas, adrenal cortical carcinoma, adrenal neuroendocrine tumours, corpus uteri carcinosarcoma; Soft tissue sarcoma of trunk and extremities, uterine sarcoma, neuroendocrine tumours of: stomach; duodenum and ampulla of Vater; jejunum and ileum; appendix; colon and rectum; pancreas; Combined chapters: ovary, fallopian tube and primary peritoneal carcinoma
No stage grouping yet assigned	Parathyroid, lacrimal gland carcinoma, conjunctival melanoma, brain and spinal cord; soft tissue sarcoma of: orbital; head and neck; abdomen and thoracic visceral and unusual site sarcoma, spine and pelvis bone sarcoma
Detailed concepts/new structure added	Sentinel node, micrometastasis, isolated tumour cells, circulating and disseminated tumour cells minimum number of lymph node harvest, essential TNM, prognostic grid, paediatric malignancies

2. Host-related: comorbidity, immunocompetence, age, gender, race, family medical background (genealogy), nutritional status, and obesity.
3. Therapy-related: Treatment is effective only if patients can tolerate the drug. To address this, the system should include factors that can predict the degree of toxicity to a particular therapy.
4. Environment-related: Access to advanced treatment can change the outcome even among similar stages of the disease.
5. Tumour-Host relationship:
   (a) Symptoms related to cancer
   e.g., Illness index: Even for the same stage of a particular disease, the symptom presentation may vary significantly. The symptoms and metabolic disturbances can very well change the treatment or at least the sequence of treatment.
   (b) Performance status
   The single-most important factor which can influence the treatment plan offered by the clinician.
   (c) Psychological status:
   e.g., Psychologic Index: Based on the effect of the disease on the psychological health.
   (Anxiety, depression, denial, suicidal and psychotic behaviour).
6. Biomarkers: Incorporation of non-linear or interactional molecular (genomic/proteomic) biomarkers into the TNM system can guide molecular biology driven treatment—an improvement over the existing TNM system based therapeutic guidelines with greater accountability for molecular tumour-host interaction.
   This inclusion may evolve a population-based 'one size fits all' model into a personalised approach based on biological determinism while retaining conventional staging's essential attributes.

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Part II

Public Health

Cancer Registration in India

Rajesh Dikshit and Atul Budukh

Abbreviations

HBCR	Hospital-based cancer registries
IARC	International Agency for Research on Cancer
PBCR	Population-based cancer registries

1 Establishing Cancer Registries

Cancer is contributing significantly to the burden of disease in India. The cancer burden in the country will continue to increase with aging population and changes in life style. In order to understand cancer burden and time trends over the years, there is a need for unbiased data that can provide such information and help in planning and evaluating cancer control measures.

In low- and middle-income countries, including India, the tools to assess disease burden via mortality statistics or routine surveillance mechanism are not available. The cancer registries are therefore very important instruments to measure cancer burden in a defined population.

Cancer registries can be classified broadly into two types: hospital-based and population-based. Hospital-based cancer registries (HBCR) collect the data on cases diagnosed/treated in a defined institution or institutions. These data are extremely useful for developing clinical care in these institutions and also in evaluating survival based on details of treatment. However, these data are not useful to assess cancer burden in the population because they are more or less biased depending upon availability of clinical services and clinicians in the hospital, and they do not capture data of all cancer cases in a given population. Thus, the burden of cancer cases in the population if estimated from hospital data will not only underestimate the burden but may not also indicate leading sites of cancer in the population as hospital data will suffer from referral bias.

Population-based cancer registries (PBCR) collect data of all cancer cases in a defined population; thus, they are able to provide burden of cancer cases in a defined population, and as cancer registration is a permanent process, they also provide information on time trends of cancer over the years. It is not possible to collect information on cancer cases by visiting each and every household or by visiting all physicians or all clinics, particularly in the urban cities. Therefore, registries prepare a list of sources of registration which can give information on cancer cases in that population. There are three major sources of registration; hospitals, laboratories (pathology and radiology) where cancer cases are diagnosed or treated, and death certificates. The sources of registration may also include hospitals that are far away from the location of registry, if the cases from registry area are going to hospitals that are far away for diagnosis/treatment. The assumption for listing these three types of sources of registration for capturing all cancer cases is that at some point cancer cases will visit these sources, which are largely cancer diagnostic centers and/or with facilities for cancer treatment. Because the cancer case may visit more than one cancer care facility, registries develop mechanisms to check the duplicates so as to count cancer cases only once, even if cancer cases get registered at many sources. When registries are established in rural areas, these assumptions are not met. The diagnostic laboratories and hospitals are not available nearby; therefore, cancer patients visit family physicians/primary health care centers or take treatment other than allopathic with available health care providers. For rural registries, therefore, primary health centers, ASHA workers, visit randomly selected households, and household survey once in 5 years is mandatory to ensure completeness of registration. Because of the unavailability of a diagnostic facility, large proportion of cases enrolled by rural registry are based on clinical confirmation.

Unlike western countries, where most of the data collection by registries is passive, i.e., registry receive the data

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from various sources electronically, in India data collection is active and partially passive. For active data collection, trained registry staff visit various sources of registration and collect information on a minimum set of variables required by registries. The requirement to set up rural and urban registries and their workflow is summarized in Table 1 and Fig. 1a, b.

The minimum variables that need to be collected by registries are implied in the purpose and definition of registry. The cancer registry's main purpose is to collect all **new cancer** cases in a defined **population, in a defined time period by age and gender**. Thus, minimum variables required for cancer registries are demographic (name, age, and gender) and residential status so as to count the person only once and to ensure that the patient is coming from the same defined population for which cancer burden is being collected. In order to make sure that we are registering only cancer cases, variables related to method of diagnosis and its details are essential. The variable on date of diagnosis is mandatory to ensure the time period when the cancer case was diagnosed. In addition, registries collect information on clinical extent of disease, and minimum treatment details are collected by most of the registries. PBCR usually do not have information on staging or treatment details because it is difficult to collect this information from various sources, which gives rise to cancer cases.

The PBCR mainly produce the following statistics:

1. **Number of cancer cases in given population**: This measure is useful to know the burden of cancer cases and thus helps in planning resources for cancer control.
2. **Crude incidence rates of cancer**: This measure takes into account population. Thus, it is a useful indicator to know how many cancer cases there are per million of population.
3. **Age-standardized rates**: This measure takes into account differences in age distribution of population. Because cancer is a disease of old age, it is important to take into account the differences in age structure of population to study the differences in the rates. This measure is mainly used to compare the rates between two populations.
4. **Truncated age-standardized rates**: This measure is equivalent to age-standardized rates but in age group generally truncated between 35 and 64 years. This is useful to compare the rates in middle ages and also to account for under-registration in cancer cases in older ages.

India does not have a national cancer registry. Many states and rural areas are underrepresented in the registry network

Table 1 Requirement for establishment of rural and urban cancer registries

Rural	Urban
• Formation of Steering committee, Identification of coordinating centre and Principle Investigator	• Formation of Steering committee, Identification of coordinating centre and Principle Investigator
• Office space of 500 sq ft, furniture, computer and internet	• Office space of 500 sq ft, furniture, computer and internet
• Trained cancer registry staff for case abstraction and coding	• Trained staff for case abstraction and coding
• Close link with the nearby registry/IARC regional Hub for technical support	• Close link with the nearby registry/IARC regional Hub for technical support
• Area (at least 10 lakhs population)	• Area (at least 10 lakh population)
• Cancer registry should be located at the Cancer Hospital, Medical college or at the district hospital	• Cancer registry should be located at the Cancer Hospital, Medical college or at the district hospital registry should be located
• List of hospitals, pathology labs, Diagnostic center's where patient visit for diagnosis and treatment	• List of hospitals, pathology labs, Diagnostic center's where patient visit for diagnosis and treatment
• Cancer treatment centers are outside the registry area (50–400 km)	• Cancer treatment center in the registry area (10–20 km)
• List of Primary health center, rural hospital, contact details of medical officer, ANM and Multipurpose workers	• NA
• List of villages and contact details of Sarpanch, ASHA workers, teacher	• NA
• Community interaction, cancer education	• NA
• Village visit, every 6 months 1 day for 1000 population for patient identification as well for confirmation	• Residence confirmation by telephone
• If require we may have to organize detection clinic	• NA
• House to house survey in 5% population for the completeness of the registration	• NA
• Death cases collection from village administrative office/house visit as well from hospital death record, follow back of death record	• Death cases collection from municipal office
• Letter from health authority to extend the co-operation to the registry staff	• Letter from health authority to extend the co-operation to the registry staff
• Steering committee	• Steering committee
• For 10 lakh population Rs. 25 lakhs	• For 10 lakh population Rs. 20 lakhs

of India. This is because of difficulties encountered while collecting the data from different sources. The major challenges in establishing the registries are lack of a proper documentation system (poor medical records), lack of basic health services (particularly in rural areas), lack of cooperation from different sources of registration to allow collation of data in a given population, and lack of trained personnel in cancer registration.

Cancer registration in India is coordinated mainly by National Cancer Registry Programme (ICMR). At present, there are 36 PBCR and 236 HBCR under National Cancer Registry Programme of India [1]. In addition, the Centre for Cancer Epidemiology at Tata Memorial Centres coordinates 19 PBCR [2–4]. The cancer registries operational in India are summarized in Fig. 2.

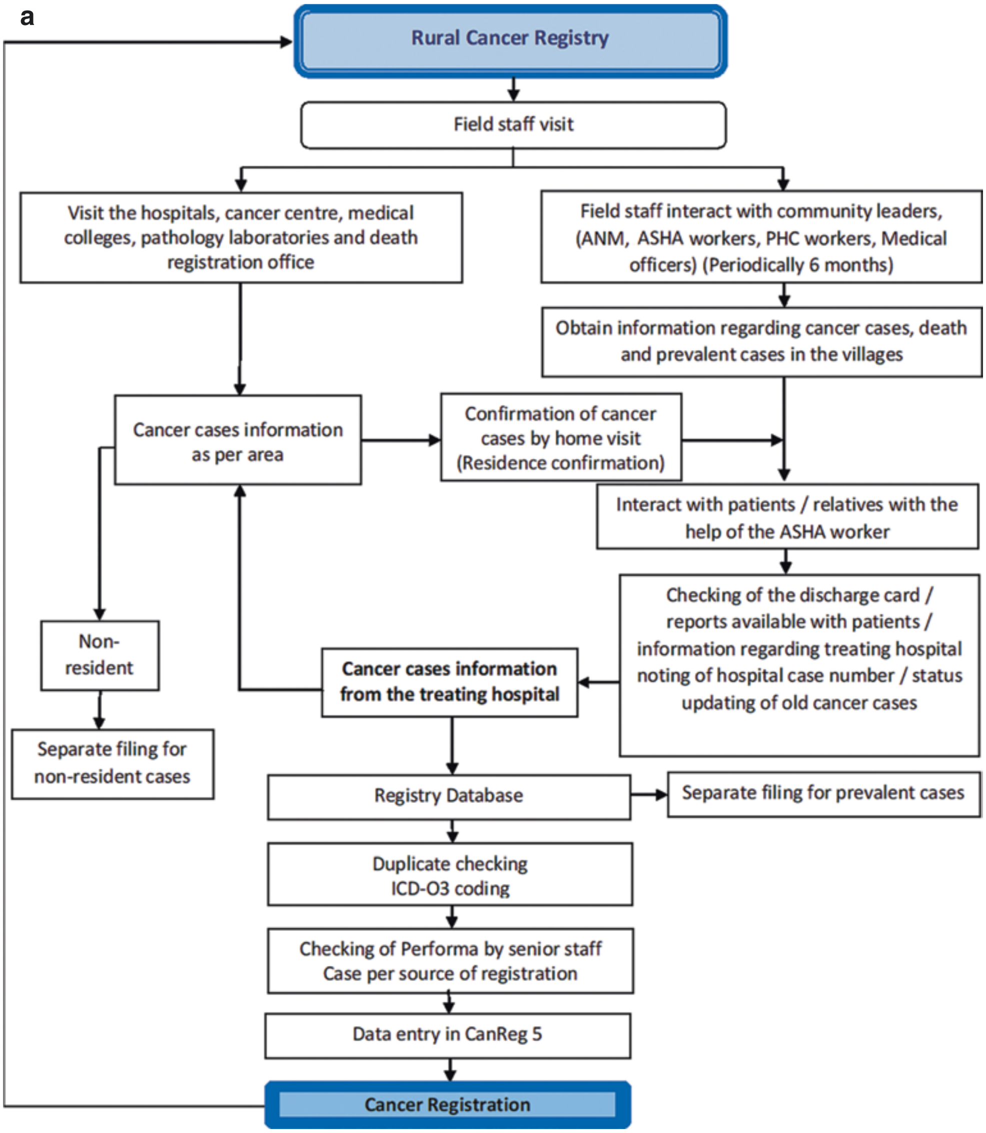
a
Rural Cancer Registry
Field staff visit
Visit the hospitals, cancer centre, medical colleges, pathology laboratories and death registration office
Field staff interact with community leaders, (ANM, ASHA workers, PHC workers, Medical officers) (Periodically 6 months)
Obtain information regarding cancer cases, death and prevalent cases in the villages
Cancer cases information as per area
Confirmation of cancer cases by home visit (Residence confirmation)
Interact with patients / relatives with the help of the ASHA worker
Checking of the discharge card / reports available with patients / information regarding treating hospital noting of hospital case number / status updating of old cancer cases
Non-resident
Cancer cases information from the treating hospital
Separate filing for non-resident cases
Registry Database
Separate filing for prevalent cases
Duplicate checking ICD-O3 coding
Checking of Performa by senior staff Case per source of registration
Data entry in CanReg 5
Cancer Registration

Fig. 1 (**a**) Work flow for rural cancer registry. (**b**) Work flow for urban cancer registry

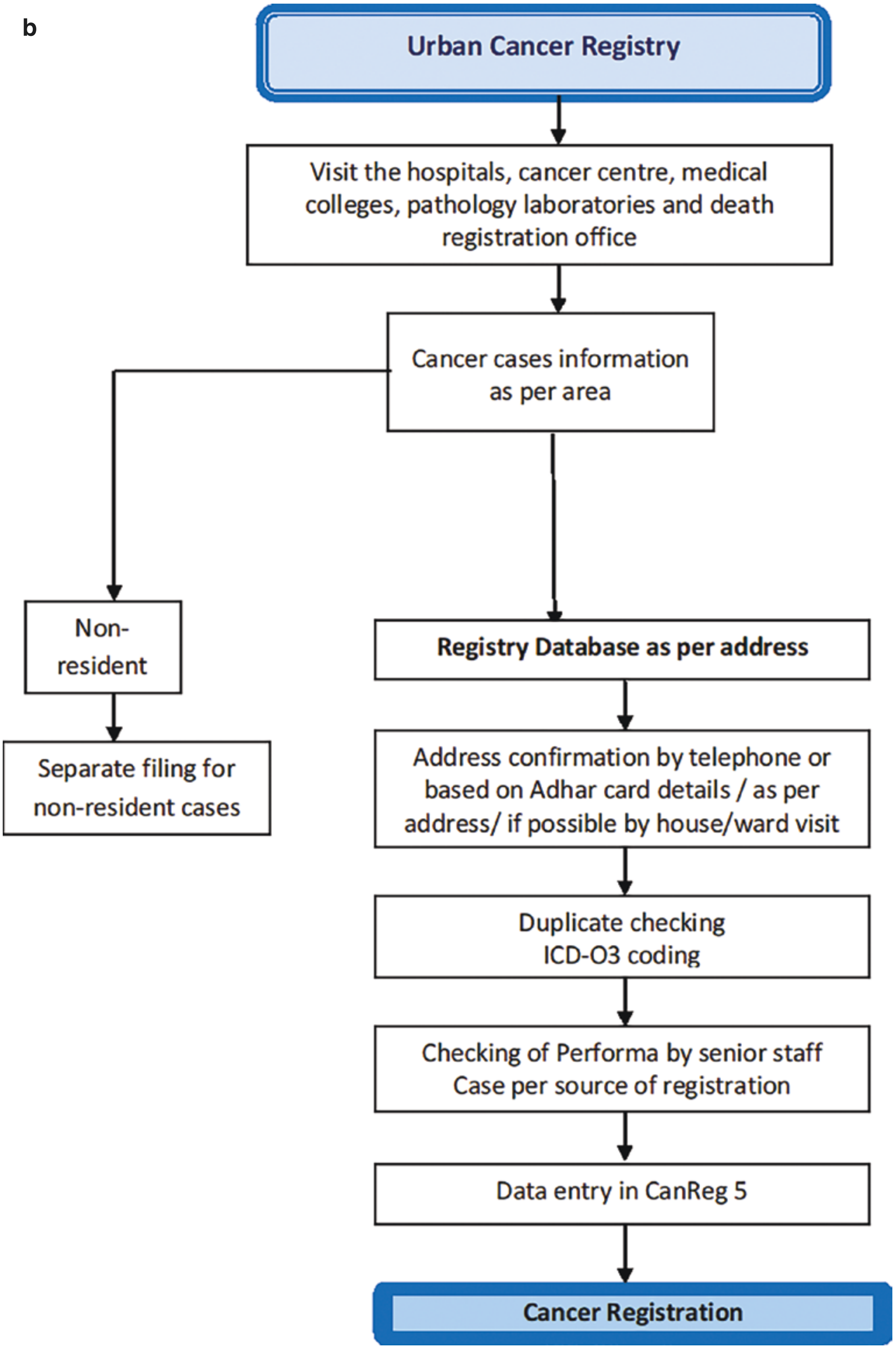
b
Urban Cancer Registry
Visit the hospitals, cancer centre, medical colleges, pathology laboratories and death registration office
Cancer cases information as per area
Non-resident
Separate filing for non-resident cases
Registry Database as per address
Address confirmation by telephone or based on Adhar card details / as per address/ if possible by house/ward visit
Duplicate checking
ICD-O3 coding
Checking of Performa by senior staff
Case per source of registration
Data entry in CanReg 5
Cancer Registration

Fig. 1 (continued)

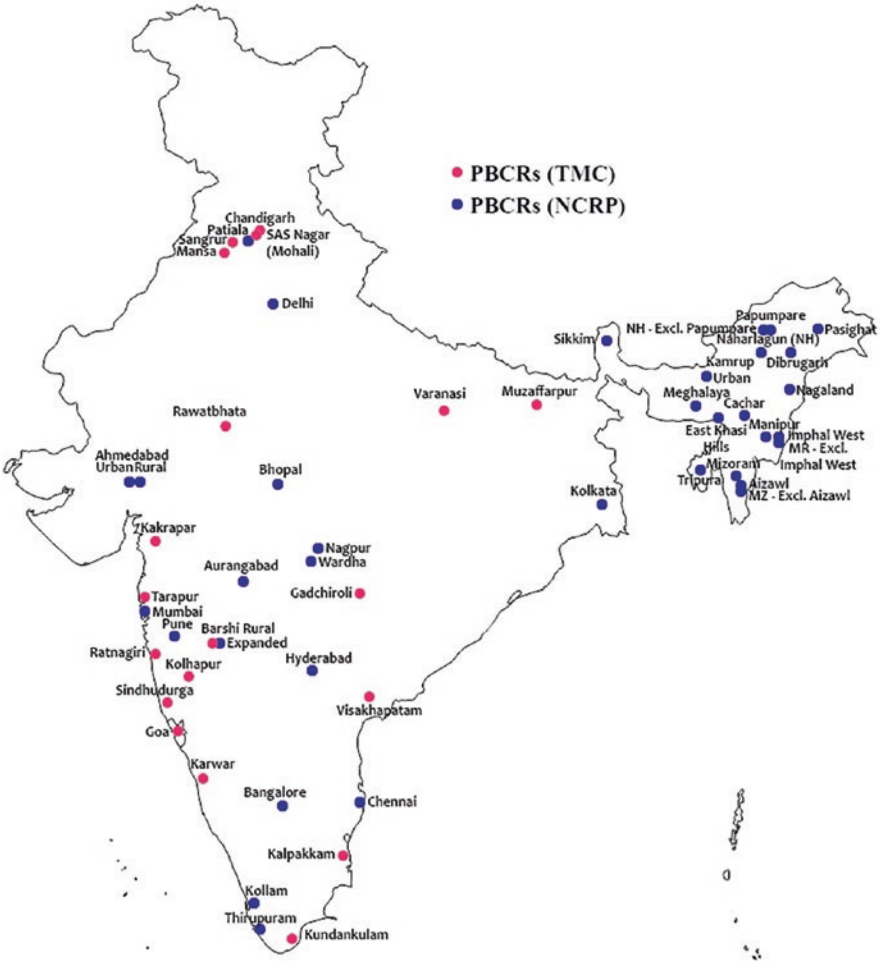
● PBCRs (TMC)
● PBCRs (NCRP)
Chandigarh
Patiala
Sangrur
Mansa
SAS Nagar (Mohali)
Delhi
Sikkim
NH - Excl. Papumpare
Papumpare
Naharlagun (NH)
Pasighat
Kamrup Urban
Dibrugarh
Meghalaya
Cachar
Nagaland
East Khasi Hills
Manipur
Imphal West
MR - Excl. Imphal West
Mizoram
Tripura
Aizawl
MZ - Excl. Aizawl
Varanasi
Muzaffarpur
Rawatbhata
Ahmedabad Urban Rural
Bhopal
Kolkata
Kakrapar
Nagpur
Wardha
Aurangabad
Gadchiroli
Tarapur
Mumbai
Pune
Barshi Rural
Expanded
Ratnagiri
Kolhapur
Hyderabad
Sindhudurga
Visakhapatam
Goa
Karwar
Bangalore
Chennai
Kalpakkam
Kollam
Thiruvuram
Kundankulam

Fig. 2 Network of population-based cancer registries in India

2 Cancer Burden in India

The cancer burden in India is estimated by two sources:

1. **GLOBOCAN**: International Agency for Research on Cancer (IARC) maintains an interactive web-based platform to provide global cancer statistics. It is updated from time to time and takes into account data of existing PBCR and extrapolates it to all over India. The GLOBOCAN estimates are based on the weighted/simple average of the most recent local rates of existing PBCR and extrapolated to all over India.
2. **Global Burden of Disease**: As a part of Global Burden of Disease initiative, cancer burden was estimated in India using data from multiple sources, including 42 PBCR and the nationwide Sample Registration System of India. Global Burden of Disease estimated the incidence and mortality from 1990 to 2016 for different states. The estimates of global burden of disease were published in *Lancet Oncology* and are close to estimates made by GLOBOCAN [5].

The GLOBOCAN 2018 estimated 1.1 million new cases of cancers (570,045 male cases and 587,249 female cases) cases in India in the year 2018 [6]. The site-wise estimates for male and females are tabulated in Tables 2 and 3. The leading cancer among males are oral cavity and lung cancer, followed by stomach, colorectal and oesophagus cancer. Among females, breast cancer is the predominant cancer, followed by cervix uteri, ovary, and oral cavity. All the registries in India have shown increase in rates of breast cancer while cervical cancer has shown substantial decrease in last 15 years in urban as well as rural registries. The five most frequent sites in India are tabulated in Table 4.

Table 2 Estimated cancer burden in India for males—GLOBOCAN 2018

ICD	Cancer	Incidence	ASR per 100,000	Mortality	ASR per 100,000
C00–06	Lip, oral cavity	92,011	13.9	50,812	7.7
C07–08	Salivary glands	3194	0.5	2412	0.39
C09–10	Oropharynx	15,529	2.5	13,006	2.1
C11	Nasopharynx	3471	0.53	2537	0.39
C12–13	Hypopharynx	20,668	3.3	6960	1.1
C15	Oesophagus	33,890	5.5	31,337	5.1
C16	Stomach	38,818	6.2	35,168	5.7
C18–21	Colorectum	36,687	5.8	28,591	4.6
C22	Liver	18,807	3.1	17,548	2.8
C23–24	Gallbladder	9884	1.6	7491	1.2
C25	Pancreas	5279	0.81	5170	0.79
C32	Larynx	25,834	4.2	15,405	2.5
C33–34	Lung	48,698	7.8	45,363	7.3
C43	Melanoma of skin	1327	0.21	1106	0.17
C45	Mesothelioma	799	0.13	751	0.12
C46	Kaposi sarcoma	44	0.01	30	0
C60	Penis	9938	1.6	6930	1.1
C61	Prostate	25,696	4.4	17,184	2.9
C62	Testis	4414	0.63	1955	0.3
C64–65	Kidney	9783	1.6	6451	1.1
C67	Bladder	14,729	2.4	8099	1.3
C70–72	Brain, central nervous system	17,300	2.6	15,234	2.3
C73	Thyroid	5432	0.83	2525	0.42
C81	Hodgkin lymphoma	5342	0.79	3454	0.53
C82–86, C96	Non-Hodgkin lymphoma	17,456	2.7	15,690	2.4
C88 + C90	Multiple myeloma	8307	1.4	6361	1
C91–95	Leukaemia	24,986	3.8	19,151	2.9
C00–97	All cancers	570,045	89.8	413,519	65.8

Table 3 Estimated cancer burden in India for females—GLOBOCAN 2018

ICD	Cancer	Incidence	ASR per 100,000	Mortality	ASR per 100,000
C00–06	Lip, oral cavity	27,981	4.3	21,804	3.4
C07–08	Salivary glands	4482	0.7	2694	0.4
C09–10	Oropharynx	2374	0.4	1947	0.3
C11	Nasopharynx	1615	0.3	1178	0.2
C12–13	Hypopharynx	5279	0.8	1844	0.3
C15	Oesophagus	18,506	2.9	15,167	2.4
C16	Stomach	18,576	2.9	16,261	2.5
C18–21	Colorectum	20,064	3.1	14,499	2.2
C22	Liver	8863	1.4	8079	1.3
C23–24	Gallbladder	16,115	2.5	12,185	1.9
C25	Pancreas	5581	0.9	5358	0.8
C32	Larynx	2887	0.5	2235	0.4
C33–34	Lung	19,097	3.0	18,112	2.8
C43	Melanoma of skin	1721	0.3	947	0.2
C45	Mesothelioma	877	0.1	826	0.1
C46	Kaposi sarcoma	48	0.0	26	0.0
C50	Breast	162,468	24.7	87,090	13.4
C51	Vulva	3446	0.5	1756	0.3
C52	Vagina	5208	0.8	2918	0.5
C53	Cervix uteri	96,922	14.7	60,078	9.2
C54	Corpus uteri	13,328	2.1	5010	0.8
C56	Ovary	36,170	5.5	24,015	3.7
C64–65	Kidney	5671	0.9	3460	0.5
C67	Bladder	4197	0.7	2132	0.3

Table 4 (continued)

ICD	Cancer	Incidence	ASR per 100,000	Mortality	ASR per 100,000
C70–72	Brain, central nervous system	10,842	1.7	8769	1.4
C73	Thyroid	13,256	2.0	2603	0.4
C81	Hodgkin lymphoma	3773	0.6	2260	0.4
C82–86, C96	Non-Hodgkin lymphoma	10,654	1.6	7820	1.2
C88 + C90	Multiple myeloma	4616	0.7	3539	0.6
C91–95	Leukaemia	17,069	2.7	13,320	2.1
C00–97	All cancers	587,249	90.0	371,302	57.5

Table 4 Leading cancer sites in India by gender: 2018

Male			Female		
Cancer site	Incidence	ASR	Cancer site	Incidence	ASR
Lip, oral cavity	92,011	13.9	Breast	162,468	24.7
Lung	48,698	7.8	Cervix uteri	96,922	14.7
Stomach	38,818	6.2	Ovary	36,170	5.5
Colorectum	36,687	5.8	Lip, oral cavity	27,981	4.3
Esophagus	33,890	5.5	Colorectum	20,064	3.1
All cancer site	570,045	89.8	All cancer site	587,249	90.0

ASR age-standardized rates

3 Regional Diversity in Cancer Burden and Type

Cancer rates and types differ in India by geographical regions. There are also rural urban differences within the geographical regions. The cancer rates are much higher in most states in North Eastern India. The rates in rural India are much lower than those reported by urban registries. The highest rates are reported by the Mizoram state cancer registry (211.5 per 100,000) while the lowest rates are reported by rural registry of Barshi (40.9 per 100,000).

The cancer rates in different PBCR are shown in Fig. 3, while regional diversity in burden and cancer types is tabulated in Table 5.

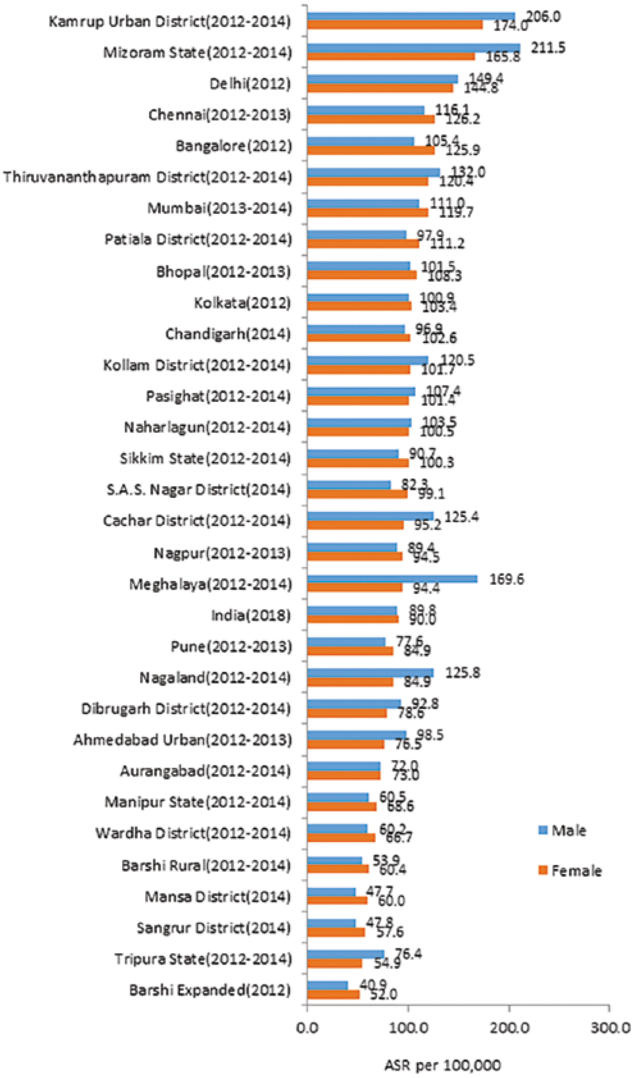

Fig. 3 Age-standardized rates in cancer registries in India—2016

Table 5 Cancer burden and leading cancer sites by region

Region	Registry	All sites		Leading sites	
		Male	Female	Male	Female
North India	Delhi	149.4	144.8	Lung (17.2)	Breast (41.0)
	(2012)			Prostate (12.4)	Cervix Uteri (15.5)
				Mouth (9.5)	Gall Bladder (11.8)
				Tongue (9.3)	Ovary (10.0)
				Larynx (8.9)	Corpus Uteri (5.5)
	Chandigarh	96.9	102.6	Prostate (12.7)	Breast (32.7)
	(2014)			Lung (10.5)	Cervix Uteri (8.0)
				Oesophagus (6.0)	Ovary (7.8)
				Larynx (5.5)	Corpus Uteri (6.9)
				Mouth (5.5)	Gall Bladder (5.4)
	SAS Nagar	82.3	99.1	Lung (7.8)	Breast (29.5)
	(2014)			Prostate (7.3)	Cervix Uteri (10.0)
				Esophagus (5.2)	Ovary (9.1)
				Urinary Bladder (5.1)	Oesophagus (6.5)
				Brain (4.6)	Gall Bladder (5.2)
	Sangrur	47.8	57.6	Oesophagus (4.7)	Breast (13.6)
	(2014)			Mouth (2.8)	Cervix Uteri (8.6)
				Tongue (2.7)	Oesophagus (5.7)
				Liver (2.4)	Ovary (3.5)
				Prostate (2.2)	Gall bladder (2.2)
	Mansa	47.7	60.0	Oesophagus (5.5)	Breast (12.5)
	(2014)			Larynx (3.0)	Cervix Uteri (11.8)
				Prostate (2.5)	Oesophagus (6.4)
				Brain, NS (2.3)	Ovary (3.6)
				Tongue (2.3)	Gall Bladder (3.0)
South India	Chennai	116.1	126.2	Lung (11.6)	Breast (37.9)
	(2012–2013)			Stomach (10.8)	Cervix Uteri (15.9)
				Mouth (8.5)	Ovary (8.2)
				Tongue (7.4)	Corpus Uteri (6.0)
				Prostate (6.7)	Stomach (5.1)
	Bangalore	105.4	125.9	Lung (11.7)	Breast (34.4)
	(2012)			Stomach (8.2)	Cervix Uteri (15.3)
				Prostate (8.2)	Ovary (6.5)
				Oesophagus (6.7)	Mouth (5.4)
				Liver (4.8)	Lung (4.9)
	Thiruvananthapuram District	132.0	120.4	Lung (16.8)	Breast (33.7)
	(2012–2014)			Prostate (9.4)	Thyroid (13.3)
				Mouth (6.6)	Cervix Uteri (7.0)
				Tongue (6.5)	Ovary (7.0)
				Rectum (5.5)	Corpus Uteri (5.1)
East India	Kolkata	100.9	103.4	Lung (19.1)	Breast (25.5)
	(2012)			Prostate (8.2)	Cervix Uteri (10.4)
				Mouth (6.8)	Ovary (8.0)
				Larynx (5.6)	Gall Bladder (7.7)
				Tongue (5.4)	Lung (7.4)
West India	Pune	77.6	84.9	Mouth (7.7)	Breast (26.4)
	(2012–2013)			Lung (6.9)	Cervix Uteri (9.0)
				Prostate (6.3)	Ovary (6.3)
				Tongue (4.0)	Lung (3.9)
				Oesophagus (3.8)	Mouth (3.7)
	Mumbai	111.0	119.7	Lung (11.4)	Breast (36.0)
	(2013–2014)			Mouth (10.1)	Cervix (8.4)

Table 5 (continued)

Region	Registry	All sites		Leading sites	
		Male	Female	Male	Female
				Prostate (9.7)	Ovary (7.4)
				Liver (7.2)	Lung (6.4)
				Lymphoma (5.9)	Corpus Uteri (4.7)
	Barshi (Rural)	53.9	60.4	Mouth (5.1)	Cervix Uteri (16.1)
	(2012–2014)			Oesophagus (4.0)	Breast (12.4)
				Liver (3.7)	Ovary (2.9)
				Rectum (2.4)	Oesophagus (2.2)
				Tongue (2.3)	Lung (2.1)
West India	Gadchiroli	49.1	59.7	Mouth (18.5)	Cervix Uteri (13.8)
	(2015–2016)			Ill-defined sec and unspecified sites (7.5)	Mouth (10.7)
				Digestive organs-other and ill defined (3.1)	Breast (6.2)
				Leukemia (2.2)	Ill-defined sec and unspecified sites (5.8)
				Tongue (2.1)	Tongue (4.2)
Central India	Bhopal	101.5	108.3	Mouth (14.3)	Breast (33.1)
	(2012–2013)			Lung (12.4)	Cervix Uteri (13.8)
				Tongue (8.4)	Ovary (8.4)
				Larynx (6.3)	Gall Bladder (6.4)
				Prostate (5.6)	Mouth (5.5)
Northeast India	Meghalaya	169.6	94.4	Oesophagus (51.2)	Oesophagus (22.7)
	(2012–2014)			Hypopharynx (15.1)	Cervix Uteri (9.6)
				Lung (12.8)	Mouth (7.7)
				Stomach (12.5)	Stomach (6.8)
				Tongue (9.2)	Breast (6.7)
	Mizoram State	211.5	165.8	Stomach (42.1)	Lung (29.3)
	(2012–2014)			Oesophagus (32.6)	Cervix Uteri (23.1)
				Lung (32.6)	Stomach (20.2)
				Liver (11.3)	Breast (19.9)
				Hypopharynx (10.2)	Oesophagus (7.6)

4 Utility of Cancer Registry Data

Cancer registries are essential for developing cancer control strategies. Cancer registries are considered as "Central Nervous System (eyes and ears) of Cancer Control Programme." The cancer registries are useful in:

1. Identification of cancer burden in population and thus guide to requirement of need of primary, secondary and tertiary facilities.
2. Identify most common cancer sites and monitor trends over the year.
3. Evaluate the success of primary and secondary prevention programme.
4. Evaluate success of treatment.
5. Generate hypothesis regarding risk factors of cancer by comparing differences and similarities in incidence rates in different population.

Examples of utilization of registry data are below:

1. **Utility of cancer registry data in building treatment facility and to eliminate fear of cancer**
   There was widespread belief in Punjab that cancer rates were very high in Punjab compared to other parts of India. Tata Memorial Centre, Mumbai thus took up the task of establishing a cancer hospital in Punjab state. PBCR were first established in rural areas, small towns, and big cities of Punjab. Registry data demonstrated that cancer rates are not very high in Punjab compared to other parts of India and provided useful information to build up the cancer hospital as per requirement of the state [7–10].
2. **Evaluating success of primary prevention programme**: In India, there is a huge tobacco control programme. The programme has resulted in reduction in the use of smokeless tobacco. In order to assess the impact of

reduction in use of smokeless tobacco on incidence and mortality over the period of time can only be evaluated by data from cancer registries [11].

3. **Evaluation screening programme**: In Mumbai, a cluster randomized trial was planned to evaluate impact of clinical breast examination on reduction in breast cancer mortality and role of visual inspection with acetic acid in reducing mortality from cervical cancer. The trial was conducted for 20 years to observe effect on mortality. PBCR in Mumbai provided important information on breast and cervical cancer mortality to evaluate its success. Similarly, the government of India has launched a screening programme for breast, cervix and oral cavity cancer in India. The impact of a nation-wide screening programme in reducing mortality for these cancer sites will be evaluated only by good-quality cancer registries [12].
4. **Evaluating changes in cancer pattern in India**: Cancer of cervix uteri was one of the most leading sites of cancer in Mumbai and other parts of India, while breast cancer rates were much lower. With changes in life style and economic transition, there were changes observed in pattern of female cancer, with cervical cancer showing sharp decline in urban and rural areas. The rise of breast cancer was observed by all registries in India over the past two decades. This information is extremely useful in planning prevention and treatment facilities for female cancer [13, 14].
5. **Generating hypothesis**: It was observed by registry data that there is a huge geographical difference in incidence of gall bladder cancer. Gall bladder cancer has high rates in the north and northeast of India, but the rates are lower in western and southern in India. A case–control study was planned by Tata Memorial Centre, Mumbai to evaluate risk factors for this fatal cancer. Factors like history of gallstones and use of contaminated mustard oil were observed as important risk factors, which guided the development of preventive strategies for gall bladder cancer in the high-risk region [15, 16].
6. **Evaluating cancer care**: The registry data have been used to measure population-based survival. This has helped in providing indication of level of cancer in different populations [17].

In India, PBCR covers around 10% of the population in India. Although many more cancer registries are required in order to obtain a more accurate assessment of cancer incidence and mortality, registries so far have provided extremely useful information that has been used by government in planning cancer control.

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Cancer Screening in India

Sharmila A. Pimple and Gauravi A. Mishra

Abbreviations

CBE	Clinical breast examination
CNBSS	Canadian National Breast Screening Study
DRE	Digital rectal examination
ERSPC	European Randomized Study of Screening for Prostate Cancer
FIT	Fecal immunochemical test
gFOBT	Guaiac fecal occult blood test
HC2	Hybrid Capture 2
HPV	Human papillomavirus
LDCT	Low-dose computed tomography
LMICs	Low–middle-income countries
MSE	Mouth self-examination
NLST	North American National Lung Screening Trial
OVI	Oral visual inspection
PBCR	Population-based cancer registry
PSA	Prostate-specific antigen
RCT	Randomized controlled trial
RR	Risk ratio
TRUS	Transrectal ultrasound
USPSTF	US Preventive Services Task Force
VIA	Visual inspection with acetic acid
VILI	Visual inspection with Lugol's iodine

1 Principles of Screening

Screening tests are primarily not diagnostic tests. Screening implies and refers to the application of a relatively simple and inexpensive test to an apparently healthy population with no overt signs or symptoms of the disease in question to identify subset of individuals who warrant additional investigation to determine the presence or absence of the particular disease in question [1].

The ultimate objective of screening for a particular disease is to bring down the mortality from that disease among the individuals subjected to the screening test. However, the true benefits of any type of screening have to be assessed by evaluating the cost of administration, its risks and the benefits that may be derived accrued by implementing it in public health programs [2].

Not only that the chosen screening modality should have documented strong evidence from randomized control trials for it being effective in decreasing mortality from cancer, but the potential benefits of organized population-based cancer screening program need to outweigh any potential harms to apparently normal people screened [3].

Thus, the essential minimum requirements for disease control program for population-based screening should be based on the determination of evidence on benefits versus risks and costs of cancer screening as adopted by the World Health Organization, which essentially takes into account (1) disease condition, (2) suitable screening test and (3) health care systems requirements [1, 4, 5].

1.1 Disease Condition

The disease in context should be an important public health problem for control. Cancer incidence or mortality rates need to be assessed for the region to warrant instituting a screening program. There has to be sufficient understanding of the natural history of the disease with recognizable pre invasive clinical phase to estimate the opportune significant window period during which the disease is detectable, and effective treatment can be instituted to justify screening.

There has to be an accepted and effective treatment for the disease if detected in the presymptomatic stage with early treatment offering distinct advantage of reduction in mortality over the late treatment that is given after the development of symptoms.

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An evidence-based treatment policy needs to be in place for disease management. Furthermore, the benefits of detecting the disease condition in a few people should outweigh the harms that can occur to people with a false-positive test, including unnecessary invasive investigations and treatment.

1.2 Suitable Screening Test

The chosen screening tests should have high level of accuracy with validated operating characteristics. The screening test must be cost-effective, safe, acceptable and convenient to administer in organized public health program settings with least discomfort and complications for people to participate for sustainable program implementation.

1.3 Health System Requirements

Target population to be screened needs to be clearly defined with respect to age, eligibility and screening intervals. Effective implementation of screening program can be accomplished if it is able to decrease the disease morbidity and mortality in the eligible target population. This requires well established referral network to access quality assured diagnostic services for the screen detected cases with accessible and adequate treatment facilities for those diagnosed with the disease including follow up of individuals treated for the disease.

1.4 Practical Concerns, Harms and Benefits from Screening

Screening programs are initiated by the health systems of the country for healthy individuals to achieve net health benefit for the communities; however, administration of the screening tests to large populations can result in unintended adverse outcomes for some individuals due to false-positive and false-negative test results. Hence, adequate information and communication of likely adverse effects as well as the potential benefits helps informed decision making for participation in the program. Regular process monitoring, evaluation and quality assurance of screening programs are vital to ensure effectiveness of the program implementation.

This chapter explores the evidence for screening effectiveness and the most resource-appropriate relevant cancer screening modalities for screening and early detection of the three most common cancers prevalent in low–middle-income countries (LMICs) like India.

2 Cervical Cancer Screening

An estimated 569,847 new cervical cancer cases and 311,365 deaths were reported worldwide in 2018 with cervix cancer as the fourth most commonly diagnosed cancer and fourth leading cause of cancer related mortality among women worldwide in LMIC countries [6].

India contributed 28% of cervical cancer mortality burden with 87,090 deaths due to cervical cancer. Cervical cancer incidence rates varied across population-based cancer registries (PBCR) in India with a mean age-standardized rate (ASR) of 14.7 per 100,000 (Globocan 2018) [7]. Papumpare district in Arunachal Pradesh (30.2), Aizawl district (28.0) and Mizoram state (23.1) in North East India reported the highest age-adjusted rates (AAR) for cervical cancer [8].

Data examining trends for cervical cancer from six PBCRs in India spanning almost two decades between 1982 and 2003 have reported significant reduction in the incidence of cervical cancer in all registries with 2% mean annual percentage change (MAPC%) over a period of time [9, 10].The decreasing trends in cervical cancer incidence in the absence of an organized screening program has been attributed to improvements in overall education and socioeconomic status of women with associated increase in age of marriage, improvements in genital hygiene and adopting family planning services [11, 12].

Cervical cancer is mostly preventable. Availability and improved access to population-based cervix cancer screening services will help further bring down the incidence and mortality due to cervical cancer in the regions.

2.1 Cervical Cancer Screening Tests

2.1.1 Cervical Cytology

Screening using the conventional Pap cytology, though, had never been rigorously tested in randomized clinical trials; however, conventional cytology-based screening programs in developed countries have reported substantial reductions in cervical cancer mortality [13].

Quality assured pap cytology test is a highly specific, with estimates of the order of 98% to 99%. Several meta-analyses however have reported low Pap cytology sensitivities for the CIN2 and CIN 3 (53% in HIC and 26–65% in LMIC) [14, 15].

Thus, due to the low sensitivity of cytology, the cervical screening benefit to the population comes only with the tests being undertaken and administered regularly at frequent intervals with high screening coverage of women and good quality assurance and monitoring of the program. In LMICs, however, organization of such systematic screening programs is not feasible for economic and socio-demographic reasons besides inadequate infrastructure and quality assurance measures. In fact, introduction of cytology screening programs in the Latin American countries like Brazil and Mexico has not demonstrated reduction in the cervical cancer burden in the region [16, 17].

In the post-HPV vaccine era, with reported nearly 90% reduction in the prevalence of cervical pre cancer lesions and based on the protection offered by the newest nonavalent vaccine there will be a significant reduction in the PPV of cervical cytology [18, 19].

A critical evaluation of the impediments in initiating cervical cytology screening programs in LMICs led to a search for alternative low-cost screening techniques that are operationally feasible and scientifically valid based upon visual inspection of the cervix, i.e., Visual inspection with acetic acid (VIA), visual inspection with Lugol's iodine (VILI) to provide cervical cancer screening services through the public health platform.

2.1.2 Visual Inspection with Acetic Acid (VIA)

VIA is simple, noninvasive and inexpensive visual test, has easy to learn approach, does not require any laboratory setup and is a real-time test with results available immediately, and even nonphysicians can be trained to perform the procedure [20].

VIA has emerged as the most cost effective, operationally suitable screening modality for LMICs with the potential for greater population coverage than other screening approaches. VIA as the most suitable alternative to cervical cytology have been evaluated for its test characteristics in several cross-sectional studies in LMICs. The pooled test characteristic estimates for VIA from the IARC lead multicenter studies conducted across India and Africa have demonstrated sensitivity in the range of 62% to 80% and specificity ranging from 77% to 84% to detect high-grade CIN lesions [21].

In a large cluster randomized trial for VIA conducted in Southern India, VIA was performed by trained nurses and has reported 25% reduction in cervical cancer incidence and 35% reduction in mortality with single round of screening by VIA [22]. Another large cluster randomized study, Mumbai, in Western India, recently reported a significant 31% reduction in cervical cancer mortality with four rounds of biennial VIA screening performed by trained primary health workers. The interobserver variability (kappa) coefficient reported in the study was 0.84 between the primary health workers and an independent examination by expert clinician. This study also reported an almost zero over-diagnosis rate, which is very crucial for overburdened public health systems in LMICs [23].

More recently, Sauvaget and colleagues, after pooling 26 studies from low- and middle-income provided summary estimate of VIA accuracy for sensitivity of 80% (range 79–82%), specificity of 92% (range, 91–92%), PPV of 10% (range 9–10%) and NPV of 99%. Factors such as region, capacity of personnel such as health worker, nurse, or physician undertaking the screening, study duration, screening settings as well as size of study population had no impact on VIA accuracy, demonstrating the overall reliability of VIA screening [19]. Another meta-analysis published earlier had reported sensitivity of VIA at 79% with lower specificity at 85% [24].

In terms of feasibility of administration, VIA test can be performed by a wide range of personnel. Since the test provides immediate results and allows for prompt referral for further diagnostic evaluation. Thus, with effective referral linkages for treatment, VIA can be a most optimal alternative to cytology screening in low-resource countries with high burden of cervical cancer to bring down the incidence and mortality due to the disease.

2.1.3 Human Papilloma Virus (HPV) Testing

Human papillomavirus (HPV) causality for cervical cancer is now been well established and is considered a necessary cause of the disease with HPV 16 and 18 accounting for 70% of cervical cancer cases. Molecular laboratory techniques to detect viral DNA or the mRNA of the E6 and E7 oncoproteins of the target oncogenic HPV types, which are highly sensitive and reproducible, are available and have been recommended in place of cervical cytology for primary cervical cancer screening. This is in addition to other potential uses of HPV testing such as triage of equivocal or low grade CIN and follow-up of women treated for high-grade CIN to determine cure rates [25].

In meta-analyses of cross-sectional studies, the sensitivity of the most commonly used Hybrid Capture 2 (HC2) DNA test was 90.4% to detect CIN2+ and 95.3% to detect CIN3+ respectively; the specificity was however consistently lower than cytology at 86.5% (95% CI = 83.1–89.8%) [26]. Results from a multicenter study in India reported the sensitivity of HPV test varying from 45.7% to 80.9% for detecting CIN 2–3 lesions across the study sites; the specificity ranged between 91.7% and 94.6% and the positive predictive value between 6.7% and 13.7% [27].

A large cluster randomized trial for cervical cancer screening in rural India evaluating VIA, conventional cytology and HPV DNA testing, reported that HPV testing alone was associated with 53% reduction in the number of advanced cervical cancers and 48% reduction in deaths with single round of screening with hrHPV testing compared with the existing standard of care of only opportunistic screening. No reduction in cervical cancer mortality was reported in the groups undergoing screening by cytology despite the strict adherence to the quality control and participant follow up procedures adopted in the study [28].

There is now consistent and robust evidence that HPV DNA detection has 20–45% greater one-time test sensitivity for high-grade CIN than cytology-based methods. HPV DNA testing has some definite advantages over the other tests in that the test being objective, reproducible with high-throughput technologies enabling to process large number of samples at the same time, with some of the test platforms delivering the results in less than 3 h. However, the test still remains unaffordable and expensive for many LMICs. The high negative predictive value (NPV) of HPV testing (nearly 100%) allows extending the screening interval up to 5–10 years. Requirement for lesser number screening rounds translates into consequent savings for the governments that can offset the possibly higher cost of the test compared with cytology [29–31].

With the upcoming HPV DNA detection platforms with the potential to deliver more simplified and point-of-care HPV tests, HPV screening offers the possibility of linking screening to treatment in a single visit, in resource constrained settings. In a randomized screening trial that investigated the acceptability and efficacy of screening women and treating those with positive tests without colposcopy and histological sampling, the study demonstrated that the HPV test screen-and-treat intervention was associated with a 3.7-fold reduction in the cumulative detection of CIN2+ lesions by 36 months against that of VIA which was associated with a 1.5-fold reduction. Thus, for every 100 women screened, the HPV DNA test screen-and-treat strategy averted 4.1 cases of CIN2+ compared to 1.8 cases averted with VIA-screen and-treat strategy [32].

2.1.4 Self-Collected Vaginal Samples

Recent years have added promising results from HPV DNA testing through self-collected samples versus that of health care personnel collected samples, with almost complete preservation of the sensitivity and specificity of the screening method.

Evidence suggests that self-HPV testing is well accepted, can be performed by women with appropriate information and instructions in the privacy of their homes and was found to be more accurate than VIA and also compared favorably with that of clinician-HPV testing for screening of cervical cancer in low-resource settings where there are challenges for women to access health facilities as well as hard to reach remote areas of the region [33, 34].

A pooled analysis of self-collected HPV testing however reported low sensitivity and specificity than testing clinician-collected samples with signal-based assays. By contrast, some PCR-based HPV tests generally showed similar sensitivity on both self-samples and clinician-based samples [35]. Self-HPV testing may complement current screening programs and also offer an opportunity to improve screening coverage in settings that do not have easy access to screening and to reach out to women not likely to participate in the regular screening program [36].

2.2 Conclusion

Both the screening modalities of HPV testing and VIA have proved to be effective in preventing cervical neoplasia and thereby deaths due to cervical cancer in clinical trials. Screening using point of care VIA test to detect precancerous lesions that can be treated cost effectively in single visits would be currently suitable in developing country settings like India. In future when affordable rapid tests for the carcinogenic types of HPV infection become available for use can be the screening tools of choice for implementation in population-based settings [37].

Results from the cost-effectiveness studies conducted across three continents from LMIC of India, Kenya, Peru, South Africa and Thailand indicate that screening approaches requiring minimal visits, including single visit strategies that combined testing and treatment are the most cost effective. Two or three screenings per lifetime, starting around age 35 years, at intervals of 5 to 10 years, with either VIA or HPV testing reduced the lifetime risk of cancer by approximately 25% to 36%, and projected to cost less than 500 dollars per year of life saved [38, 39].

Since many low-resource settings do not have optimal infrastructure and capacity for cervical cancer treatments, screening and early detection through organized screening program with timely treatment of cervical precancerous lesions before they become invasive with high screening coverage are necessary for reducing morbidity and mortality due to cervical cancers. Health policymakers, public health program managers and health professionals responsible for recommending the most suitable country-level cervical cancer prevention and screening strategies for public health program implementation need to design and integrate comprehensive cervical cancer prevention and control within the larger initiative for the control of noncommunicable diseases utilizing and training the existing manpower and health infrastructure resources with in the country.

3 Breast Cancer Screening

Breast cancer is the most common cancer and most common cause of cancer related death among women globally and in India. An estimated 2,088,849 new breast cancer cases were diagnosed globally in 2018, accounting for 24.2% of all female cancers and the fourth leading cause of death due to cancers in females with nearly 626,679 women deaths due to breast cancer [7, 40]. With 162,468 new cases, the age-standardized incidence rate for breast cancer was reported at 24.7 per 100,000 in India [7].

Incidence of breast cancer has been rising at the rate of almost 5% per year has been observed among urban women in low- and middle-income countries (LMICs), where rates were historically low. The rising trends have been attributed to life style changes in the childbearing patterns, increased adoption of western lifestyles and dietary choices in urban and semiurban regions. Mortality rates are continuing to remain high in LMICs since majority of the women continue to present in the late-stage of the disease largely due to very limited screening, diagnostic and treatment capacities in these regions [41, 42].

Thus, implementing appropriate screening measures for detecting asymptomatic disease and early diagnosis of symptomatic disease, which is further facilitated by appropriate treatment, are essential components of breast cancer control strategies.

3.1 Mammography

Mammography for breast cancer screening has been the most widely used screening modality, in high-income countries with evidence of benefit for women aged 40 to 74 years. Other screening tools such as clinical breast examination (CBE) and breast self-exam (BSE) have also been evaluated across but are of uncertain benefit. Technologies such as ultrasound, magnetic resonance imaging, tomosynthesis and molecular breast imaging are being evaluated, usually as adjuncts to mammography.

The evidence for efficacy of mammographic screening was established mainly from randomized controlled trials (RCTs), in which women were randomized to mammographic screening at regular intervals or no screening. Based on the outcomes of these trials, IARC estimated a 25% reduction in breast cancer among women between age 50 and 69 years and 19% in women age 40 and 49 years. The results were consistent across studies among older women but were inconsistent among women in their forties [43–49].

Evidence suggests that mammography screening performed every 12 to 33 months is effective in decreasing breast cancer mortality. Benefit from screening by mammography is largely due to regular biennial screening. The estimates for women who need to be screened to save a life are 1904 for ages 39–49; 1339 for ages 50–59 and 377 for ages 60–69, respectively [43].

Accuracy of screening mammography is largely dependent two main factors, patient factors related to age, breast density use of hormone replacement therapy and factors related to radiology instrumentation along with training of the radiologist whose performance varies substantially depending on the training and level of experience [47, 48].

Also, the demonstrated benefit of mortality reduction by mammography screening is likely to be outweighed by the risk of harm due to false-positive findings or the potential for overtreatment of nonaggressive biologically favorable early-stage disease [49, 50].

Harms from screening vary with patient age, life expectancy and tumor type (ductal carcinoma in situ and/or invasive) [51, 52]. Though the estimates of over diagnosis vary widely, from less than 5% to more than 50%, nearly 54% of the overall breast cancers detected by screening mammograms are estimated to be due to overdiagnosis [53]. In the follow-up of the long-term CNBSS and well-conducted excess incidence studies in the United States [54] and Scandinavia [55, 56] at least 20% of screen-detected breast cancers were overdiagnosed.

Though women across all age group subjected to mammography screening witness false-positive test results, overdiagnosis and unnecessary earlier treatment; however, false-positive results are more common among women aged 40 to 49 years, whereas overdiagnosis is a greater concern for women in the older age groups [57], On an average, 10% women are likely to be recalled after each screening mammography for further testing, and only 5 of the 100 women recalled are likely to have cancer [58].

According to the Cochrane Review, assuming that mammography screening reduces breast cancer mortality by 15% with rates for overdiagnosis and overtreatment at 30%, it means that for every 2000 women invited for screening throughout 10 years, one will avoid dying of breast cancer and 10 healthy women, will receive unnecessary treatment, who otherwise would not have been diagnosed if they had not been screened. Also another 200 women will be subjected to psychological distress and uncertainty for extended duration because of false-positive findings. With substantial advancements in breast cancer treatment modalities and greater awareness toward early detection of breast cancers since the trials were carried out, it is most likely that the absolute benefit of screening today is much smaller than in the trials. Recent observational studies have shown more overdiagnosis than in the trials and nonsignificant or no reduction in the incidence of advanced cancers with breast cancer screening [49].

Cost-effectiveness analysis carried out by the WHO and partners in various middle-income countries showed that mammography screening was not cost-effective for a lower-middle income country [59].

Since mammographic screening requires considerable infrastructure and costs, screening with clinical breast examination (CBE) and breast self-examination (BSE) has been under consideration in LMICs.

3.2 Clinical Breast Examination (CBE)

Until recently, two randomized control trials assessing CBE alone as a screening tool, were on-going in India [60, 61], out of which results of the Mumbai Study, led by Tata Memorial Centre, which is one of the largest and oldest trial with biennial CBE that was offered four times in one arm versus no screening in the other arm in its final study results has reported a significant reduction in mortality of nearly 30% in women aged ≥50. No significant reduction in mortality was seen in women younger than 50 years [61].

CBE earlier has been used in conjunction with mammography in one Canadian trial, and as the comparator modality versus mammography in another trial. Based on the 25-year follow-up from the Canadian National Breast Screening Study (CNBSS), an RCT of breast cancer screening [62], annual mammography does not reduce breast cancer mortality beyond that of CBE or usual care.

CBE accuracy depends on the provider skills with optimal training in using proper standard technique, and the measure of its sensitivity and specificity, therefore, has bearing on harms due to false-positive results leading to additional testing and anxiety as well as false-negative results with potential for false reassurance and delay in cancer diagnosis. Specificity of CBE in women aged 50 to 59 years was 88% to 99%, yielding a false-positive rate of 1% to 12%. Sensitivity is higher with longer duration, proper techniques and quality training by the trained personnel [63].

As per the current evidence, CBE may be more efficacious, practical and cost-effective option in LMICs, since it can be performed by nonmedical, trained health care workers and combined with timely effective treatment, can further bring down breast cancer mortality at the population level.

3.3 Breast Self-Examination (BSE)

BSE is the examination performed regularly by the women themselves after receiving appropriate instructions to perform systematic examination of the entire breast for a lump or other change in the breast that is suggestive of cancer. Most evidence for the efficacy of BSE comes from two randomized trials from Saint Petersburg [64] and Shanghai [65] where BSE was compared with usual care (no screening activity) and has not been shown to reduce breast cancer mortality [66, 67].

In both of the completed BSE trials, the group that received instructions to perform BSE reported more benign breast lesions than in the control groups suggesting that formal instruction to perform BSE leads to more breast biopsies and diagnosis of more benign breast lesions with biopsy rate of 1.8% among the study population compared with 1.0% among the control group [66]. Both the IARC working group and the US Preventive Services Task Force concluded that the efficacy of BSE remains to be proven [68].

3.4 Ultrasonography

Ultrasonography is not a primary screening modality, its primary role lies in the diagnostic evaluation of palpable or masses identified on mammography. A consensus statement by the European Group for Breast Cancer Screening on screening of breast cancer using ultrasound examination concluded that ultrasound is an adjunct to mammography and clinical examination in the further assessment of both palpable and nonpalpable breast abnormalities. At the population level, screening of asymptomatic women by the use of ultrasound was associated with very high rates of both false-positive and false-negative results. Hence, they found little evidence to support the use of ultrasound in population breast cancer screening at any age [64]. Less than 3% of women with lump will ultimately be found to have breast cancer, in the setting of normal mammography and ultrasonography [65, 69–71].

3.5 Conclusion

Resource constrained settings, where mammography screening is not cost-effective or feasible and majority of women are diagnosed in late stages with breast cancer should optimize the available resources for ensuring access to women with symptomatic lesions to health services for early diagnosis and treatment. With the recent evidence form the Mumbai Breast cancer screening study, low-cost screening approaches such as CBE, seems to be a promising approach for developing country settings [61, 72].

In addition to the LMIC's barriers of literacy and education among women about awareness of breast cancer, its risks, perception and misconceptions toward diseases in general need special focus. Development of culturally relevant, appropriate local education programs for Breast health awareness emphasizing value and benefits of early detection in improving breast cancer outcome and saving lives are critical to improving population coverage and participation in early detection programs [73].

4 Oral Cancer Screening

Globally, lip, oral cavity cancers accounted for an estimated 354,864 new cases and 177,384 deaths in 2018. World age-standardized incidence rate (ASIR) per 100,000 for Lip, oral cavity cancer as per the GLOBOCAN 2018 estimates were 4.0 with age-standardized death rate (ASDR) rates of 2.0. With 119,992 new cases, India reported lip, oral cavity cancer with ASIR of 9.1 for both sexes combine and 13.9 among males. Lip and oral cavity cancers thus were the top-ranked cancers among males and the second highest malignancy in both the sexes with equally high mortality rates of 9.2 (ASDR) [74]. In India, 5-year survival is estimated at less than 35% [75].

Any form of tobacco use and excessive alcohol use are the major risk factors for oral cavity cancer. The relatively high prevalence of oral cancer in India is mainly attributed to the use of the smokeless tobacco products and consumption of betel quid with or without tobacco [76, 77]. Human Papilloma Virus (HPV) has been shown to be another independent risk factor for oral squamous cell carcinomas (OSCC) of the base of the tongue, tonsils, pharynx and larynx [78–81].

Despite the ease of performing the oral cavity inspection during routine physical and dental examination, oral cancers are still detected in very advanced stages of disease resulting in poor prognosis. Early detection of oral pre cancer lesions can significantly reduce the currently high mortality rate attributable to oral cancer. Oral cancer has a well-documented long preclinical phase, starting with an oral preinvasive lesion (OPL) consisting of potentially malignant disorders such as leukoplakia, submucous fibrosis, erythroplakia, that progresses through the increasing degrees of dysplasia, and finally develops into invasive oral squamous cell carcinoma (OSCC). These OPL can be clinically detected through careful visual inspection and palpation of the oral cavity. Early detection would not only significantly improve the cure rate and thereby reduce mortality, but it would also lower the cost and morbidity associated with treatment of late stage oral cancers [82].

Robust evidence is needed to select the most suitable screening tool with required criteria of being highly specific and sensitive, cost effective and therefore economically viable for implementation in population screening programs.

4.1 Oral Cancer Screening Tests

4.1.1 Oral Visual Inspection (OVI)

A conventional oral visual inspection (OVI) of the oral cavity, using normal (incandescent) light, has long been the standard method for oral cancer screening. The UK working group on screening for oral cancer and precancer in the 1990s had concluded that the most suitable screening for oral cancer and precancer is a thorough and systematic examination of the oral cavity conducted with good lighting [83]. OVI has been widely evaluated for its efficacy, ease of administration and acceptability to detect oral precancerous lesions and cancer including cost-effectiveness studies in low-income settings in reducing oral cancer mortality [84–92].

OVI is a subjective test and being provider dependent, its test performance in detecting precancerous lesions and early asymptomatic oral cancers had sensitivities ranging from 60% to 97% and specificity ranges from 50% to 99% [84–87]. A meta-analysis reported an overall sensitivity of 0.85 (95% CI 0.73, 0.92) and specificity of 0.97 (95% CI 0.93, 0.98) indicating a satisfactory test performance for an oral examination [88].

Trials in India of oral visual inspection to detect lesions by trained health workers have shown pooled sensitivity of 87.90% and specificity of 92.05% [89–91]. A significant 34% reduction in oral cancer mortality was demonstrated among a high-risk group of tobacco or alcohol users following three rounds of oral visual screening in a cluster-randomized controlled trial in India [91]. The same study from India with 15-year follow-up results found sustained reduction in oral cancer mortality, There was a 81% reduction in oral cancer mortality (95% CI 69–89%) in tobacco and/or alcohol users complying with all four rounds of screening [92].

This was the first evidence from a cluster randomized control trial to provide the efficacy of an oral cancer screening program, suggesting good evidence for oral visual examination in reducing mortality rate of oral cancer in high-risk individuals. Population-based screening program could result in diagnoses of oral cancer at an earlier stage of disease with improved survival rates [93]. The cost-effectiveness study that used data from a randomized clinical trial in India provides evidence that oral cancer screening with oral visual inspection by trained health care workers can be administered under U.S. $6 per person in a screening program. The incremental cost per life-year saved was U.S. $835 for the all-screened population and U.S. $156 in the high-risk population using tobacco, indicating cost-effectiveness of screening even in LMIC settings [94].

Although OVI could be considered as an effective screening test, there are still many limitations with this approach since the vast majority of the precancer lesions detected are benign and a very small proportion of lesions are progressive or become malignant. Thus, since OVI cannot discriminate between potentially premalignant lesions from lesions not likely to progress to cancer, the potential harms of oral visual screening therefore include requirement of additional diagnostic investigations, with added burden on health care system for conducting incisional or excisional biopsy leading to detection and treatment of biologically insignificant conditions that may have no impact on oral cancer incidence.

4.1.2 Mouth Self-Examination and Other Screening Methods

Mouth self-examination (MSE) using a mirror has been evaluated as a screening test in some studies [95–97]. However, MSE achieving reductions in oral cancer mortality is not known. MSE was evaluated in a study involving 34,766 subjects in India and was found to have low sensitivity of 18%, while the specificity was 99.9% [98].

There is currently insufficient evidence to recommend the use of any other oral screening tests, such as toluidine blue staining, chemiluminescence, tissue fluorescence imaging, fluorescent spectroscopy, salivary analysis and oral cytology for primary screening of oral cancer [93, 99–101].

A multifaceted approach that integrates primary prevention strategies for tobacco and alcohol control with appropriate health education including tobacco cessation and secondary prevention, focused on high-risk individuals, are likely to be cost-effective and affordable in LMICs. At the same time, investing in health services to provide screening and early diagnosis services, and timely treatment for those diagnosed with invasive cancer will help attain the goal of decreasing the burden of oral cancer along with addressing disparities and inequalities in providing the population level services in the regions where it is most needed.

5 Other Cancers

5.1 Prostate Cancer Screening

Prostate cancer is the second most common cancer among men globally and accounts for 15% of all the cancers in men. The incidence is noted to be high in the more developed regions, because of widespread usage of prostate-specific antigen (PSA) testing and subsequent biopsy. In India, there are 19,095 new cases of prostate cancer annually accounting for 4% of all cancers among men [102].

The screening tests for prostate cancer include the digital rectal examination (DRE) and the PSA blood test. Thereafter the diagnostic confirmation is carried out by transrectal ultrasound (TRUS) guided biopsy. Cochrane Review [103] included meta-analysis of five studies [104–108] that did not demonstrate any statistically significant reduction in prostate cancer specific mortality risk ratio (RR) 1.00, 95% confidence interval (CI) 0.86–1.17. Also meta-analysis of the two low risk of bias studies, the European Randomized Study of Screening for Prostate Cancer (ERSPC) [104] and the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial [106] indicated no significant reduction in prostate cancer-specific mortality (RR 0.96, 95% CI 0.70–1.30). Only one study (ERSPC) reported a 21% significant reduction of prostate cancer-specific mortality in a prespecified subgroup of men aged 55 to 69 years [104].

The independent role of DRE has not been evaluated till date. Prostate cancer screening is associated with harms of over diagnosis and overtreatment due to high rate of false-positive results for the PSA test. All these result in subsequent biopsies and harms associated with it, like infection, bleeding and pain. Since any reduction in prostate cancer-specific mortality may take up to 10 years to accrue [103], it has been recommended that men having life expectancy of less than 10 to 15 years should be informed about uncertainties, risks and potential benefits associated from screening for prostate cancer. The current American Cancer Society guidelines [109] recommend that prostate cancer screening should not occur without an informed decision-making process. Men at average risk should receive this information beginning at age 50 years. Men in higher risk groups should receive this information before age 50 years.

5.2 Lung Cancer Screening

Globally, lung cancer is the most common cancer and cause of cancer related death among men as well as among both sexes combined together [110]. The majority of lung cancer cases are attributed to cigarette-smoking and have the highest mortality rate of all cancers. However, early-stage nonsmall cell lung cancers (NSCLC) have been reported to have better prognosis and which can be treated with surgical resection [111, 112].

Most cases of lung cancer present at advanced stages. Previous studies have investigated the role of screening for the detection of preclinical disease [113–115] with chest X-ray screening with or without sputum cytology. Most of the studies were focused on high-risk smokers and have so far concluded that early detection of lung cancer does not improve disease-specific mortality [116, 117].

Low-dose computed tomography (LDCT) for early stage detection of lung cancer has been studied in the recent years. It is found to be more sensitive testing modality than the chest radiography [118–120]. A large uncontrolled study demonstrated ability of LDCT to detect lung cancers at an early resectable stage [121]. The North American National Lung Screening Trial (NLST) the largest trial (n = 53,454) compared annual LDCT screening with chest radiography. In this study, annual screening with LDCT was associated with a significant reduction in lung cancer mortality among high-risk individuals (RRR = 20%, P = 0.004) aged 55 to 74 years with 30 pack-years or more of smoking. The study also reported reduction in all-cause mortality in the LDCT screening group compared with the chest x-ray group (RR 0.94, 95% CI 0.88–1.00, P = 0.04) [122].

The NLST results showed a sensitivity of 93.8% and specificity of 73.4% for LDCT [123]. Routine LDCT screening incurs the harms of false-positive findings with unnecessary workup, intervention and exposure to radiation.

The US Preventive Services Task Force (USPSTF) has recommended annual lung cancer screening in adults aged 55 to 80 years with LDCT, who have a history of 30-pack-years of smoking who currently smoke or have quit within the past 15 years [111]. The American Cancer Society since 2013 began recommending screening for lung cancer with

LDCT in high-risk patients who meet the NLST criteria [124].

There is currently insufficient data on the cost effectiveness of lung cancer screening that account for the frequency of screening, the benefits and harms (such as false-positives and overdiagnosis) to provide any recommendations for large-scale population screening programs. According to the Cochrane Review, screening with either annual plain chest radiography in smokers and nonsmokers, or more frequent chest radiography screening in smokers and ex-smokers, is not effective at reducing lung cancer mortality and hence not recommended for clinical practice [122].

5.3 Colorectal Cancer Screening

Adenocarcinoma of the colon and rectum (colorectal cancer, CRC) globally, colorectal cancers are the third most common cancers for both sexes put together. In India, colorectal cancers are the fourth most common cancers among men and the third most common cancers among women [125].

Screening tests for colorectal cancer screening involve fecal occult blood testing (FOBT) like guaiac fecal occult blood test (gFOBT), fecal immunochemical test (FIT), sigmoidoscopy and colonoscopy. All the above modalities are effective in reducing mortality, through detection and removal of adenomatous polyps and treatment of early-stage cancer. Modeling studies provide evidence to suggest that population screening programs between the ages of 50 and 75 years using any of the three screening modalities will be equally effective in terms of life-years gained [126].

Cochrane review suggests that FOBT screening reduces the risk of colorectal cancer mortality. However, no difference in all-cause mortality between the screened and non-screened populations was reported [127].

The USPSTF recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy or colonoscopy in adults, beginning at age 50 years and continuing until age 75 years. The following screening interval are suggested: (1) high-sensitivity fecal occult blood testing annually, (2) sigmoidoscopy every 5 years combined with high-sensitivity fecal occult blood testing every 3 years and (3) screening colonoscopy at 10 years interval [128].

The risks and benefits of these screening methods largely vary with minimal harm for fecal tests to the use of invasive modalities like sigmoidoscopy or colonoscopy adopted initially or in the evaluation sequence [129]. Potential harms arise from additional diagnostic procedures for lesions found incidentally, which may have no clinical significance. The risks for perforation associated with screening CT colonography in research settings are estimated to be 0 to 6 per 10,000 CT colonography studies [130]. Due to low incidence rates there is no recommendation for routine screening for CRC in India.

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Part III

Hematological Malignancies

Adult Lymphoblastic Leukemias

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Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
APML	Acute promyelocytic leukemia
APTT	Activated partial thromboplastin time
ATRA	All-trans-retinoic acid
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CR	Complete remission
HCL	Hairy cell leukemia
HDAC	High-dose cytarabine
MPO	Myeloperoxidase staining
MRD	Minimal residual disease
NSE	Nonspecific esterase
PS	Peripheral smear
PT	Prothrombin time
TT	Thrombin time
WBC	White blood cell

1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a neoplastic disease resulting from the uncontrolled clonal proliferation of myeloid precursor cells that infiltrates the blood, bone marrow and other tissues. Resultant disruption of normal haematopoiesis leads to infection and bleeding. Early and risk adapted treatment are crucial in the management of AML. Overall prognosis remains guarded with 5-year survival rate ~30% [1].

1.1 Incidence and Epidemiology

SEER database reports an incidence of 4.3 per 100,000 persons/year. No prevalence data is available from India.

Data from TMH, Mumbai, in a series of more than 2500 patients with acute leukemia, attributed 38.3% of all leukemia to be AML of which 75% were adults [2, 3]. There is an increased male preponderance and the median age of presentation is 40 years [4].

Risk factors for developing AML:

1. Genetic syndromes specially those involving DNA repair, bone marrow failure syndromes, Li Fraumeni, Downs syndrome, *RUNX1* mutation and Klinefelter's syndrome.
2. Radiation exposure.
3. Smoking.
4. Prior therapy with alkylating agents, 5–7 years post therapy, typically preceded by myelodysplastic marrow while topoisomerase II inhibitors have no preceding MDS and develop AML rather rapidly (within 2 years of therapy).
5. Antecedent hematological malignancies specially MDS and chronic proliferative disorders (polycythemia vera, myelofibrosis and essential thrombocythemia) can contribute up to 15% of adult AML (>60 years) [5].

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1.2 Clinical Presentation

1. Marrow failure/infiltration: bone pain, fatigue and dyspnoea related to anemia, infections especially perianal, pulmonary and cutaneous sites, and bleeding.
2. Hyperleukocytosis: altered sensorium, headache, dyspnoea and hypoxia.
3. Fever, weight loss, hepatosplenomegaly, lymphadenopathy (AML M5).
4. Extramedullary deposits (chloromas): cutaneous nodules, periorbital swelling, gum hypertrophy (AML M5).

1.3 Diagnosis and Classification

Chiefly, AML is classified by two systems namely, FAB and more recently, WHO as tabulated below.

WHO 2008 [6] classification is more complex involving cytogenetic and molecular typing of leukemia into 25 different types (Table 1).

1.4 Investigations

1. Complete blood count (CBC) and peripheral smear (PS)
2. Cytochemistry—Myeloperoxidase staining (MPO), non-specific esterase (NSE)
3. Bone marrow examination—Aspirate and biopsy. Bone marrow biopsy is essential in all cases as presence of clusters of blasts is also diagnostic of AML
4. Immunophenotyping—Flow cytometry

Mandatory—The markers in bold are lineage defining markers

- Immaturity marker—CD45, CD34, HLA-DR
- Myeloid Cells—CD13, CD33, CD117, CD11b, CD15, **AMPO**
- Monocytic Markers—CD14, CD36, CD64, CD11c
- Megakaryocytic—**CD41, CD61**
- Erythroid—CD105, CD71, CD235a
- Plasmacytoid dendritic cells—high expression of **CD123 and HLA-DR**

5. Cytogenetics
   (a) Fluorescent in situ hybridisation (FISH) for risk stratification as shown in Table 2
   (b) Conventional karyotyping—For detecting complex abnormalities and monosomal karyotype
6. Molecular testing
   (a) *NPM1* and *CEBPA* mutations
   (b) *FLT3* internal tandem duplication (*FLT3*-ITD)
   (c) Next generation sequencing if available for *RUNX1*, *ASXL1* and *TP53* mutation, etc.

Table 1 2008 WHO classification with 2016 modification

I	**AML with recurrent genetic abnormalities**	
	1	AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1 (AML1-ETO)
	2	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	3	APL with PML-RARA and variant translocations
	4	AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	5	AML with t(6;9)(p23;q34.1); DEK-NUP214
	6	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
	7	AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1
	8	AML with mutated NPM1
	9	AML with biallelic mutations of CEBPA
	a	AML with mutated RUNX1 (provisional)
	b	AML with BCR-ABL1 (provisional)
II	**AML with myelodysplasia-related changes**	
III	**Therapy-related myeloid neoplasms**	
IV	**AML, NOS has the following entities**	
	1	AML with minimal differentiation
	2	AML without maturation
	3	AML with maturation
	4	Acute myelomonocytic leukemia
	5	Acute monoblastic/monocytic leukemia
	6	Pure erythroid leukemia
	7	Acute megakaryoblastic leukemia
	8	Acute basophilic leukemia
	9	Acute panmyelosis with myelofibrosis
V	**Myeloid sarcoma**	
VI	**Myeloid proliferations related to Down syndrome**	
	1	Transient abnormal myelopoiesis (TAM)
	2	Myeloid leukemia associated with Down syndrome
VII	**Blastic plasmacytoid dendritic cell neoplasm**	
VIII	**Acute leukemias of ambiguous lineage**	
	1	Acute undifferentiated leukemia
	2	Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); BCR-ABL1
	3	MPAL with t(v;11q23.3); KMT2A rearranged
	4	MPAL, B/myeloid, NOS
	5	MPAL, T/myeloid, NOS

Reference: Daniel A. Arber, Blood (2016)

Diagnosis is established when marrow blast count of >20% except for AML with there current genetic abnormalities t(15;17), t(8;21), inv(16), or t(16;16).

Flow cytometry of bone marrow aspirate or immunohistochemistry on biopsy can subtype AML (see Table 2). Cytogenetic and molecular typing of AML is listed in Table 3.

1.5 Evaluation and Risk Stratification

Apart from tests required for diagnosis, laboratory tests for organ function (liver and renal function), TLS parameters (serum electrolytes including phosphorus and calcium) and

Table 2 ELN 2017 risk stratification

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD (<0.5)
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD$^{\text{high}}$[a]
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{\text{low}}$[a] (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[b]
	Cytogenetic abnormalities not classified as favourable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype[c], monosomal karyotype[d]
	Wild-type *NPM1* and *FLT3*-ITD$^{\text{high}}$[a]
	Mutated *RUNX1*[e]
	Mutated *ASXL1*[e]
	Mutated *TP53*[f]

Reference: Hartmut Dohner, Blood (2017)

viral markers (anti-HIV/anti HCV/HBsAg/anti HBcIgG) are also performed. Baseline NCCT thorax is preferred to assess for fungal infection prior to starting therapy. ECHO and ECG in all patients is required as all receive anthracycline-based chemotherapy. Peripherally inserted central catheters (PICC) is preferred for long-term venous access.

1.6 Management of AML

1.6.1 Supportive Care for AML

Nearly 30% of the patients present with infection at diagnosis [4]. Most common source of infection are blood stream, mucosal especially perianal site, skin/soft tissue and lung. Though quinolone prophylaxis is recommended [7], each institute may decide antibiotic prophylaxis as per sensitivity pattern. In our institution we do not use antibiotic prophylaxis. All patients with neutropenia (disease- or therapy-related) are at risk of fungal infections. All patients must receive antifungal prophylaxis. We use posaconazole 5 mL (200 mg) thrice daily with weekly drug monitoring to maintain appropriate drug levels. Hand washing (patient and care givers), personal hygiene (using antibiotic body wipes thrice daily and bathing) and dental care is mandatory. All patients at risk of HBV reactivation must receive prophylaxis with entecavir/lamivudine.

Use of myeloid growth factors in the induction period may increase leukemic blasts and delay platelet recovery but it reduced the duration of neutropenia by 2–5 days. Post consolidation GCF is routinely used until neutrophil recovery.

Platelet and packed cell transfusions is required throughout induction. At least two granulocyte donors should be screened at the start of induction. HLA typing should be done in intermediate and high-risk patients.

1.7 Treatment of AML

Therapy of AML is divided into two parts, i.e. induction and consolidation. All patients with intermediate or adverse risk category should be evaluated for allogeneic stem cell transplant (HSCT).

Fitness for intensive induction chemotherapy is determined by age (<65 years) and factors like infections and comorbidities. Induction regimens most commonly is “3+7” that is 3 days of an intravenous anthracycline: daunorubicin at a dose of at least 60 mg/m^2 or idarubicin 12 mg/m^2; or mitoxantrone 12 mg/m^2, and 7 days of continuous infusion cytarabine (100–200 mg/m^2) through peripherally inserted intravenous catheter.

Consolidation therapy is given to those who have attained morphological remission after induction. High-dose cytarabine (HDAC) at 2000 mg/m^2 twice daily (total of 6 doses) is given over 5 days for 3–4 cycles. These patients are at high risk of neutropenic infections and require GCSF support and clinical evaluation till count recovery.

Consolidation with allogeneic HSCT should be done in patients with intermediate/adverse risk factors.

In FLT3/ITD, Tab. Midostaurin 50 mg BD from day 8 to day 21 of induction, during HiDAC day 8–day 21 of each cycle.

Maintenance 50 mg BD 14 days of 28 days (start after day 35, after recovery post-cycle 3 HIDAC) for 12 months. To maintain ANC >1000, plt count >1 lakh should be given [8].

1.7.1 Treatment of AML in Elderly Patients

AML in elderly patients is usually a high risk (therapy-related, secondary to MDS or associated with poor-risk cytogenetic abnormalities). Patients more than 65 years or who are unfit for intense chemotherapy can be given treatment as below depending on their general condition:

1. Hypomethylating agents like azactidine or decitabine + BCL2 inhibitor venetoclax

2. SA Hypomethylating agent
3. CPX-351 (liposomal cytarabine + daunorubicin in 5:1 ratio)

Relapsed/refractory AML have poor prognosis. They should be evaluated for early allogenic HSCT. Re-Induction with intermediate-dose cytarabine, FLAG-IDA (fludarabine/cytarabine/idarubicin) or CLAG (cladribine/cytarabine) with GCSF are common salvage regimens.

1.8 Response Assessment and Monitoring

Response evaluation with bone marrow aspirate and biopsy is done usually on day 21 post induction by when there is evidence of peripheral count recovery. Complete remission (CR) is defined when marrow blast <5%, no extramedullary disease (if present at baseline), regression of splenomegaly, recovery of counts, ANC >1000/mm^3 and platelet count ≥100 × 10^9/L. Minimal residual disease (MRD) is assessed using flow cytometry and should be <0.1%. Cytogenetic or molecular abnormality should also be assessed post induction. If MRD is positive, then bone marrow examination is repeated after first consolidation. Primary refractory AML is diagnosed when bone marrow is not in remission after two courses of induction treatment.

1.9 Prognosis and Outcomes

The expected outcomes in AML are influenced by various factors, with an average 5-year overall survival of 40–50%.

1.10 Summary and Practice at TMH (See Table 3)

Table 3 Cytogenetic and molecular typing of AML

Diagnosis	Bone marrow aspirate-morphology, flow cytometry, cytogenetic and next generation sequencing and biopsy
Induction	"3+7" 3 days of an IV daunorubicin 60 mg/m^2; 7 days of continuous infusion cytarabine 100 mg/m^2 through PICC
Consolidation	Three cycles of high-dose cytarabine (HDAC) at 2000 mg/m^2 twice daily day 1, 3, 5 every 21 days
Relapsed AML	CLAG regimen followed by HSCT or if HSCT is not feasible to continue 3 HIDAC consolidation followed by observation.

2 Acute Promyelocytic Leukemia

Acute promyelocytic leukemia (APML) is a biologically distinct subset of acute myeloid leukemia (AML), which is characterized by t(15;17) translocation resulting in the PML-RARα′ gene, and has unique sensitivity to all-trans-retinoic acid (ATRA) and arsenicals.

2.1 Incidence and Epidemiology in India and Global

About 7–8% of all adult AML cases is comprised of acute promyelocytic leukemia. It is most commonly seen in middle-aged people with a median age of 47 years and is very rare before the age of 20. The incidence is slightly higher in males than females.

2.2 Clinical Presentation in India and Global

Patients with APML frequently present with symptoms arising due to complications of pancytopenia, which includes infections of variable severity, tiredness, weakness and/or hemorrhagic tendencies such as menorrhagia, gingival bleeding, ecchymoses or epistaxis. Patients can rarely present with hyperleucocytosis. More than 50% of patients have pronounced coagulation disorders including a high risk of life-threatening intracerebral hemorrhages.

2.3 Evaluation and Work-up

Suspected APML case should undergo immediate evaluation of

1. Complete blood count, to look for thrombocytopenia, TLC count to categorize APML into high risk or low risk and haemoglobin to look for transfusion requirement.
2. Peripheral blood smear will show abnormal promyelocytes with intense myelo-perioxidase activity.
3. Coagulation profile, PT/INR, APTT, serum fibrinogen level.

Only patients with pancytopenia should undergo bone marrow aspiration and biopsy. In patients with TLC more than 10,000/cumm, peripheral blood should be sent for morphology, cytogenetics, flow cytometry, FISH for t(15,17), RT PCR for PML-RARA transcripts.

Bone marrow is hypercellular, and promyelocytes account for almost all the cells. The typical abnormal promyelocyte can have varying morphology with creased, folded, kidney-shaped nuclei with prominent nucleoli, with pres-

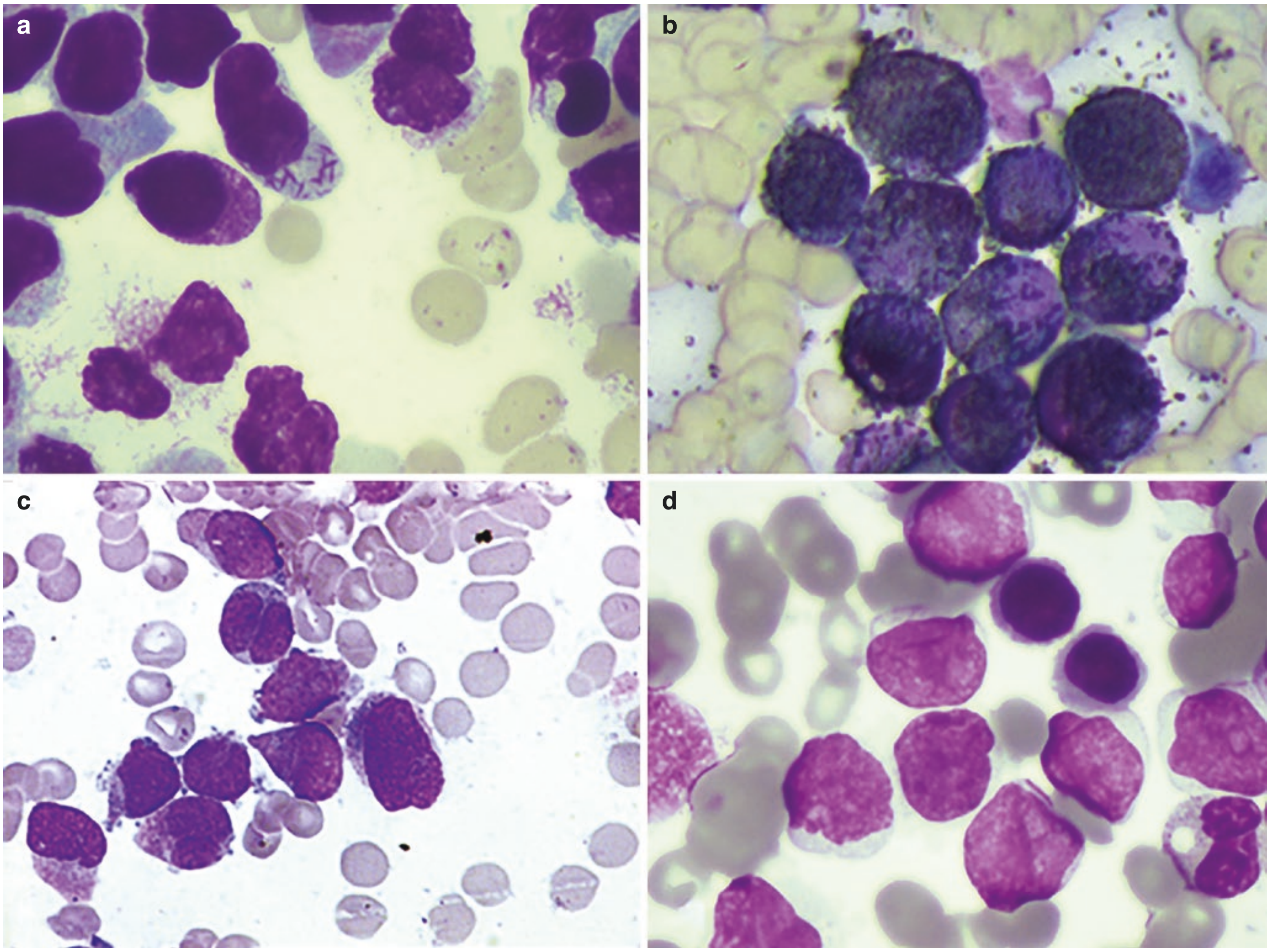

Fig. 1 Various morphology of APML. (**a**) Hypergranular APML with faggot cells. (**b**) Myeloperoxidase staining of the same. (**c**) Abormal promyelocytes with apple core type of nucleus. (**d**) Hypogranular variant of APML

ence of violet granules (which coalesce to form Auer rods) in the cytoplasm. The abnormal promyelocytes can show presence of multiple auer rods called faggot cells which if seen is highly specific for APML. The hypogranular variant (Fig. 1) may not show granules and can appear similar to monoblasts. The hallmark is that all the abnormal cells are positive for cytochemical MPO.

2.3.1 Immunophenotyping

The classic variant express bright cytoplasmic myeloperoxidase (MPO), CD13 and CD33; are usually negative for CD34 and HLA-DR. APML cells also express abnormally low levels of CD15 and weak or variable CD117. The hypogranular variant shows a similar phenotype with a comparably bright MPO expression and frequent co-expression of CD2.

2.3.2 Cytogenetics

The hallmark of APML is a translocation involving *RAR*α′, the retinoic acid receptor alpha locus on chromosome 17. 90% of APML cases contain t(15;17)(q24.1;q21.1). However, several variant translocations involving *RAR*α′ have been identified, including t(11;17) and t(5;17), which are invariably resistant to ATRA.

Fluorescence In Situ Hybridization

FISH for PML/RARA fusion (Fig. 2) is most commonly used and is quicker than conventional cytogenetics. However, both RARA fusion probes and break apart probes have to be used to screen.

Conventional Karyotype

Conventional karyotype can detect rare molecular subtypes of APML and other additional coexistent cytogenetic abnormalities; however, it has a likelihood of missing cryptic translocations.

2.3.3 RT-PCR for PML-RARA RNA

This test helps in confirming the diagnosis of acute promyelocytic leukemia (APML)based on the PML-RARα fusion product of the translocation. It also helps to identify the type

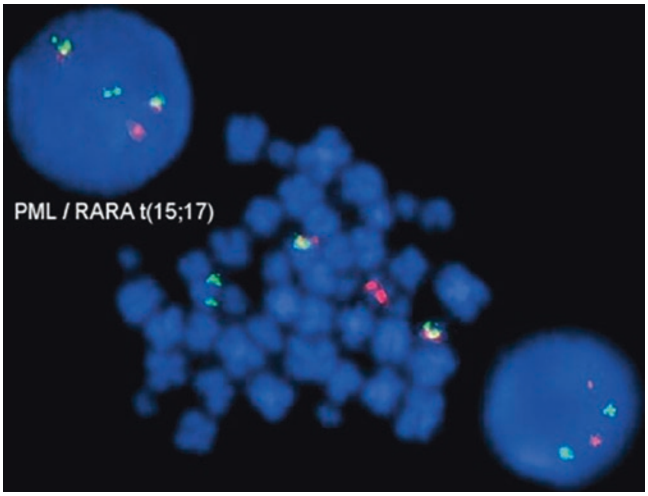

Fig. 2 The interphase cell (round nuclei) and metaphase showing yellow orange fusion signal from green and red probes for PML-RARA fusion

Table 4 Risk-stratification—Sanz score

	Low risk	Intermediate risk	High risk
Leukocytes/μL	<10,000	≤10,000	>10,000
Platelets/μL	>40,000	≤40,000	

Reference: Miguel A. Sanz, Blood (2004)

of transcript for monitoring minimal residual disease. In a small subset of patients, the RT-PCR can pick translocations missed by FISH. The RT-PCR will miss variant translocations if present. NGS can be done to detect additional mutations.

A combination of FISH and RT-PCR gives the best yield to confirm the diagnosis of APML.

2.4 Risk Stratification (Table 4)

2.4.1 Principles of Management

APML is a medical emergency, having a high rate of early mortality, often due to hemorrhage from a characteristic coagulopathy. It is vital that treatment is initiated for all patients without delay y as soon as the diagnosis is suspected based on peripheral smear, before definitive confirmation. On the other hand, arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) can be discontinued if the diagnosis is not confirmed and the treatment modified to that used for other AML types.

Differentiation therapy (ATRA) is the cornerstone treatment in the management of APML and remains as the front line agent in all modern regimens. The concurrent administration of ATRA with cytotoxic chemotherapy results in complete remission in 80–95% of patients. ATO demonstrates synergistic action with ATRA, by inducing differentiation of the malignant myeloid clone by dissociating the PML/RAR-alpha-RXR complex from the target genes.

2.4.2 Medical Management and Monitoring

The treatment comprises of several stages and may span 1–2 years.

- Remission induction
- Consolidation
- Maintenance

Induction-Low- or Intermediate-Risk APL

ATO (0.15 mg/kg) plus ATRA (45 or 25 mg/m^2) as induction is recommended. As compared to ATRA plus anthracyclines, it causes lesser toxicity, fewer deaths during induction therapy, fewer relapses and reduced risk of secondary leukemia. ATO can also be used as monotherapy with encouraging results.

Induction-High-Risk APML

ATO + ATRA + chemotherapy approach: ATO with cytoreductive therapy (Hydroxyurea) should be started on day 1. Once the confirmation by FISH for PML-RARA is available, three doses of anthracyclines like Idarubicin 12 mg/m^2 or Daunorubicin 45 mg/m^2 or Mitoxantrone 12 mg/m^2 is added on alternate days, or Gemtuzumab Ozagamycin 9 mg/m^2 which causes further cytoreduction. Leucopheresis is contra-indicated in APML due to the risk of fatal hemorrhages. ATRA is added once the differentiation is settled at around day8 (ALLG approach).

ATO alone approach is restricted to non-high-risk APML.

ATRA + chemotherapy approach has shown to be effective in several studies with complete remission rates around 90–95%. As ATRA is highly differentiating agent, we avoid using it at the start of therapy.

Prophylactic use of steroids (Inj. Dexamethasone 10 mg BD) can prevent differentiation syndrome with careful monitor for any signs of infection and blood glucose levels.

Monitoring During Induction

1. Blood counts should be monitored daily.
2. Prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen level, thrombin time (TT) should be monitored daily until stable, then weekly once.
3. ECG should be monitored twice weekly for QTc prolongation along with.
4. Renal, liver function tests, serum calcium, serum phosphorous and serum magnesium levels.

Blood product transfusion is crucial during induction to prevent bleeding or life-threatening haemorrhages. Platelets should be maintained above 30,000/μL for all patients. If the patient has differentiation or pulmonary or GI bleed, then platelets should be maintained above 50,000/μL. In case of intracranial bleed, maintain platelets above 1 lakh/μL.

To maintain haemoglobin ≥8 g/dL, packed cell should be transfused.

In case of derangement of PT/APTT, fresh frozen plasma should be given at a dose of 15 mL/kg and in case of prolonged thrombin time or low fibrinogen, cryoprecipitate should be given.

Other Issues During Induction

Differentiation Syndrome

Differentiation syndrome is a serious complication with APML that develops after the initiation of differentiating agents. This is mediated by a cytokine release storm which is characterized by fever, rise in counts, disseminated intravascular coagulopathy, hypotension, weight gain due to fluid retention, peripheral or pulmonary oedema hypotension and multi-organ dysfunction which can be fatal, if not promptly recognized. High-dose intravenous corticosteroids are helpful in such cases.

Idiopathic Intracranial Hypertension or Pseudotumor Cerebri

Idiopathic intracranial hypertension or pseudotumor cerebri is a known complication of ATRA, characterized by headaches, papilledema and increased intracranial pressure in the absence of infection or hydrocephalus. The treatment options available for patients with persistent symptoms are corticosteroids, carbonic anhydrase inhibitors (acetazolamide) and analgesics. Also reducing dose of ATRA to 25 mg/m^2 has shown to decrease the adverse effects of ATRA without decreasing its efficacy (Shanghai group).

Response Assessment After Induction

Bone marrow examination for morphology, FISH for t(15,17), RQPCR for PML-RARA for molecular remission is done at the end of induction, prior to starting consolidation to assess for hematological response. If RQPCR for PML-RARA is positive post induction, it is to be repeated post consolidation. According to the new ELN guidelines, achievement of molecular response at the end of consolidation corresponds to complete response without minimal residual disease.

Consolidation

Following confirmation of hematological CR, consolidation is given. Consolidation therapy is administered totargetleukemia cells that survived induction chemotherapy but are not detectable by conventional tests.

Non-High-Risk APML Consolidation

After induction with ATRA plus ATO: 4 courses of ATO (0.15 mg/kg/day, 5 days a week, 4 weeks on and 4 weeks off) + 7 courses of ATRA (45 or 25 mg/m^2) 2 weeks on and 2 weeks off are recommended.

High-Risk APML

After ATO + ATRA + chemotherapy induction: Consolidation is similar to non-high-risk APML protocol.

After ATO-based induction: Consolidation consists of two to three cycles of anthracycline plus ATRA.

Maintenance

For low-intermediate patients, maintenance can be safely omitted. In high-risk cases, maintenance with ATRA, 6-MP and methotrexate for approximately 18 months can be considered.

2.5 Prognosis

APML is a highly curable malignancy. More than 90% of patients with APML obtain a hematologic CR with induction therapy followed by a molecular CR after consolidation therapy. The predominant cause of induction failure (5–10%) is death from hemorrhage or infection, and it is extremely uncommon to have primary drug resistance in APL. The 3-year relapse-free survival of low risk, intermediate risk and high-risk patients are 98%, 89% and 70%, respectively.

2.6 Management of Resistant/Refractory Disease

Resistant or refractory APML is diagnosed in those patients who do not attain a molecular remission following consolidation chemotherapy. Relapse occurs in 10–15% of patients with APML and in 20–30% of those with high-risk APML. The treatment is generally aimed at achieving remission followed by high-dose chemotherapy and autologous hematopoietic cell transplantation. The choice of therapy depends on the previous therapy used and the timing of relapse. Early relapse (<6 months) cases previously treated with ATRA and ATO are treated with anthracyclines-based regimen. Patients with no prior exposure to ATO and late relapses (>6 months) are treated with ATO-based regimens. The consolidation is with stem cell transplant: autologous in those with molecular remission and allogeneic transplant in those with molecular persistence after consolidation.

2.7 Management for APML (Fig. 3)

2.8 How We Do It at TMC

At our centre, low- to intermediate-risk patients are treated with ATRA plus ATO induction followed by maintenance with ATRA plus ATO. High-risk patients are treated with ATO+ ATRA + Anthracycline followed by ATO/ATRA consolidation like non-high-risk APML protocol. Relapsed patients are managed based on previous treatment, timing of relapse, social support and finances.

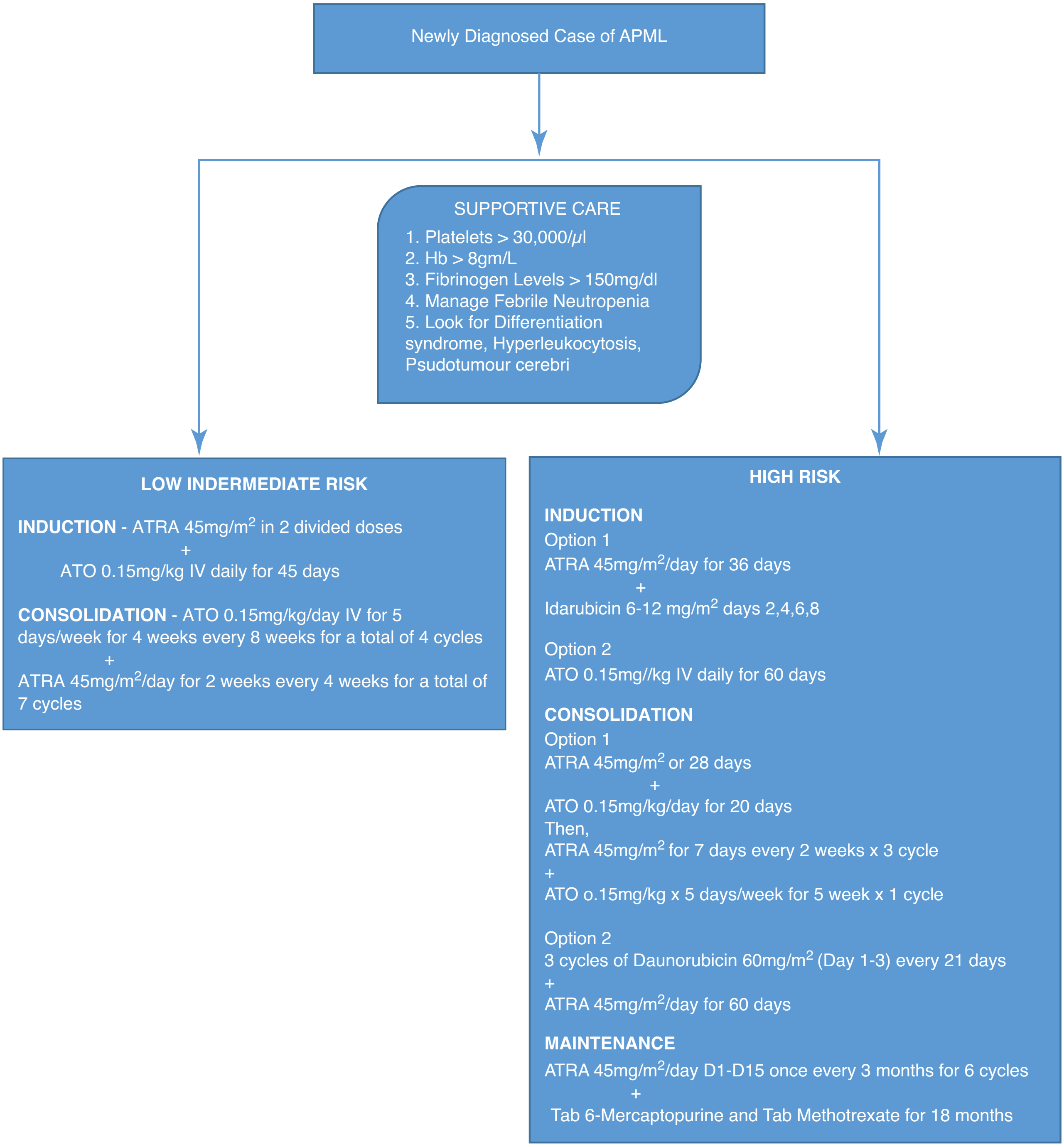
Newly Diagnosed Case of APML
SUPPORTIVE CARE
1. Platelets > 30,000/µl
2. Hb > 8gm/L
3. Fibrinogen Levels > 150mg/dl
4. Manage Febrile Neutropenia
5. Look for Differentiation syndrome, Hyperleukocytosis, Psudotumour cerebri
LOW INDERMEDIATE RISK
INDUCTION - ATRA 45mg/m2 in 2 divided doses
+
ATO 0.15mg/kg IV daily for 45 days
CONSOLIDATION - ATO 0.15mg/kg/day IV for 5 days/week for 4 weeks every 8 weeks for a total of 4 cycles
+
ATRA 45mg/m2/day for 2 weeks every 4 weeks for a total of 7 cycles
HIGH RISK
INDUCTION
Option 1
ATRA 45mg/m2/day for 36 days
+
Idarubicin 6-12 mg/m2 days 2,4,6,8
Option 2
ATO 0.15mg//kg IV daily for 60 days
CONSOLIDATION
Option 1
ATRA 45mg/m2 or 28 days
+
ATO 0.15mg/kg/day for 20 days
Then,
ATRA 45mg/m2 for 7 days every 2 weeks x 3 cycle
+
ATO o.15mg/kg x 5 days/week for 5 week x 1 cycle
Option 2
3 cycles of Daunorubicin 60mg/m2 (Day 1-3) every 21 days
+
ATRA 45mg/m2/day for 60 days
MAINTENANCE
ATRA 45mg/m2/day D1-D15 once every 3 months for 6 cycles
+
Tab 6-Mercaptopurine and Tab Methotrexate for 18 months

Fig. 3 Management algorithm for APML

3 Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) encompasses a heterogeneous group of disorders. It is characterized by uncontrolled clonal proliferation of lymphoid cells and their progenitors in the bone marrow, blood and extramedullary sites. Adult ALL constitutes ~20% of all cases. The overall disease prognosis is poor in adults as compared to children. Long-term survival with different regimens is expected to be around 40–50%.

3.1 Incidence and Epidemiology

ALL accounts for 2% of lymphoid malignancies in the USA. No data from India exists regarding incidence/prevalence of the disease.

A retrospective study from CMC Vellore showed median age to be 26 years. About 75% of cases were B cell ALL. CNS disease was seen in 12.5% while testicular involvement was seen in <1%.

3.2 Clinical Presentation

Symptoms of bone marrow failure (weakness, infections and bleeding manifestations), bone pain or joint pain, weight loss, night sweats, hepatomegaly, splenomegaly and lymphadenopathy are the common presentation of the disease. T-ALL may present with a mediastinal mass causing superior vena cava obstruction. CNS involvement will present as cranial nerve palsies (most commonly VI, VIII) or meningismus and is seen in 5–10% cases at baseline.

3.3 Evaluation and Work-Up

1. Complete blood count with peripheral smear: to look for hyperleukocytosis, thrombocytopenia or anemia. Peripheral smear shows myeloperoxidase negative blasts.
2. Renal function test, serum electrolytes including calcium and phosphorus to look for tumour lysis syndrome.
3. Viral markers (HIV serology, anti HCV, HBsAg and HBcIgG).
4. Liver function test and LDH.
5. Bone marrow studies:
   - Morphology, flow cytometry for diagnosis of B or T cell ALL.
   - Cytogenetics: FISH for diagnosis of Philadelphia chromosome or Ph like ALL. And for further risk stratification.
   - Molecular test or NGS: to know the transcript in Ph+ cases or to diagnosis Ph like ALL.
6. CSF cytology and flow cytometry are also needed to know CNS disease status. These investigations will help in diagnosis and risk stratification of the patient.
7. Sperm cryopreservation can be considered in younger males.

As per age and comorbidities, other tests of fitness for chemotherapy are advised. HLA testing of siblings and patient should be done in all high-risk patients.

3.4 Risk Stratification

The following are the adverse prognostic factors:

Age	>35
Baseline WBC	B ALL >30,000 T ALL >1 lakh/μL
Immunophenotype	Pro B ALL, early T cell
Cytogenetics	t(4,11) t (9,22) Hypodiploidy (<44 chromosomes) Complex karyotype (>5 abnormalities)
Therapy response	Time to CR >4 weeks
MRD	>0.01 at 3–6 months after initiation of therapy
Emerging risk factors	
Immunophenotype	CD20
Molecular	BAALC, FUS, ERG, IKZF1, Ph like ALL

3.5 Principles of Management

Patients are divided first as per age. Younger patients (<40 years) are treated with pediatric ALL like protocols and older individuals are treated with adult protocols. The treatment is also based on Philadelphia chromosome status. Patients in whom Philadelphia chromosome is present are treated with the addition of tyrosine kinase inhibitor (TKI).

Treatment for adult ALL can be divided into three phases: Remission induction, consolidation and maintenance. Various protocols are available more or less with same treatment philosophy, e.g. BFM protocol, CALGB protocol, UKALL protocol, etc. All these protocols are not compared head to head but have similar 5-year overall survival of ~40%.

The backbone of induction comprises of steroids, vincristine, L-asparaginase and anthracyclines. CNS prophylaxis in form of intrathecal chemotherapy are part of induction in some protocol while some others have cyclophosphamide and cytarabine. In CD 20 positive cases, Inj Rituximab at 375 mg/m^2 has shown to have 2 years EFS of 65% versus 52% in control arm.

For developing country like ours, we have to balance toxicity of treatment with disease control. In one series it has been shown that in India intensifying treatment regimens does not improve overall survival.

At the end of induction, response assessment with bone marrow flow for MRD, cytogenetics and molecular (RQPCR for BCR ABL in case Ph+ ALL) are done. PETCT is done in case of a mediastinal mass as a presenting feature in T-ALL/LBL.

The consolidation phase is aimed to keep the disease at minimal residual disease level for a prolonged period. 6

Mercaptopurine, methotrexate, cytarabine, cyclophosphamide, etc. are used. For a high-risk patient, consolidation may consist of allogeneic haematopoietic stem cell transplant. Consolidation phase also consists CNS-directed therapy consisting of high-dose methotrexate or cytarabine.

Reintensification phase is a part of consolidation. Which is similar to induction phase but with non-cross resistant chemotherapy agents. Cranial irradiation is given in this phase for CNS prophylaxis.

The maintenance phase is given for 2–3 years with low-dose chemotherapy like 6-mercaptopurine, steroids, methotrexate and vincristine. Ensuring compliance and adequate myelosuppression is a key.

CNS-directed therapy is part of all the protocols either in form of intrathecal methotrexate, intrathecal cytarabine, triple intrathecal chemotherapy, high-dose methotrexate, high-dose cytarabine or cranial irradiation.

In Philadelphia chromosome-positive patients, early addition of tyrosine kinase inhibitor has shown ~90% complete remissions. Dasatinib is preferred over imatinib due to its enhanced efficacy and better CNS penetration.

Day 8 blast count and bone marrow studies at end of induction are done to prognosticate the patient further. It also helps to decide on consolidation strategy.

Allogenic transplant is indicated in all high-risk patients like in those with hyperleukocytosis at baseline, Philadelphia or MLL translocation, ETPALL, CNS-positive disease, minimal residual disease (MRD) positive at end of induction. Though indicated in many, only a very small fraction can undergo a transplant in our setup.

3.6 Supportive Care

Managing toxicity and reducing treatment-related mortality is an important key to treatment in developing countries. Tumor lysis syndrome, hyperleucocytosis, dyselectrolytemia, bacterial infection, fungal infection, viral infection, L-asparaginase induced thrombotic events, methotrexate-related renal injury, etc. are all life-threatening toxicities. Close watch and prompt treatment are needed during these situations. Other common toxicities are raised sugars, constipation, SAIO, peripheral neuropathy, cytopenias, fatigue, anorexia, post-intrathecal chemotherapy headache.

The social and financial support system is as essential as medical treatment.

3.7 Management of Recurrent Disease

Relapse is divided as per duration of remission into very early, early and late. Prognosis of relapsed/refractory patient is guarded. Salvage by multi-agent chemotherapy followed by allogeneic transplant is the only curative option. A significant proportion of patients opt for supportive care only as an option after relapse.

3.8 How We Do It at TMC

We treat patients aged <60 years with modified BFM 90 protocol in a multidisciplinary setting. The treatment of elderly patients is individualized. TKI (Imatinib 600 mg or Dasatinib 100 mg) are added to the chemotherapy regimen in Ph-positive ALL with omission of L-asparaginase. Six weekly doses of Inj Rituximab 375 mg/m^2 is added to BFM 90 protocol in CD20 positive cases. Allogeneic stem cell transplant is considered in high-risk disease.

4 Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a clonal disorder of haematopoietic progenitor cells, caused by an acquired genetic defect in a pluripotent stem cell. The disease is caused due to constitutively active tyrosine kinase B-cell receptor (BCR)-ABL1, resulting from the translocation between chromosome 9 and 22 t(9;22)(q34; q11), which is cytogenetically detected as the Philadelphia (Ph) Chromosome.

4.1 Incidence and Epidemiology of CML in India and Global

The incidence of CML is comparable worldwide with an annual rate of 1.6–2.0 patients per 100,000 persons. Similarly in India, the annual incidence of CML was reported to be 0.8–2.2 per 100,000 population. The median age at diagnosis is 66 years, and has a slight male predominance (2.2:1.3). A recent study from the Mumbai Cancer Registry specifically examined CML and reported an age adjusted rate (AAR; per 100,000) of 0.71 in males and 0.53 in females.

4.2 Clinical Features

- Asymptomatic raised counts
- Easy fatigability
- Anorexia
- Abdominal discomfort
- Early satiety
- Weight loss
- Leukostasis–dyspnoea, priapism
- Rarely bleeding, thrombosis, gouty arthritis

Table 5 WHO definition for stages of CML

CML phase	WHO definition
Chronic phase	Peripheral blood blasts fewer than 10% in the blood and bone marrow
Accelerated phase	• Blasts 10–19% of white blood cells in peripheral and/or nucleated bone marrow cells • Basophils equal to or more than 20% of total nucleated cells • Persistent thrombocytopenia (<100 × 10^9/L) unrelated to therapy or • Persistent thrombocytosis (>1000 × 10^9/L) unresponsive to therapy • Increasing white blood cells and spleen size unresponsive to therapy • Cytogenetic evidence of clonal evolution
Blast crisis	Peripheral blood blasts ≥20% of peripheral blood white blood cells or nucleated bone marrow cells; extramedullary blast proliferation; and large foci or clusters of blasts on bone marrow biopsy

Reference: Daniel A. Arber, Blood (2016)

4.3 Signs

- Pallor
- Splenomegaly
- Sternal tenderness
- Rarely hepatomegaly
- Lymphadenopathy

CML has three phases, which are listed in Table 5.

4.4 Evaluation and Risk Stratification

4.4.1 Blood and Bone Marrow Examination

1. Complete blood count: In the chronic phase of CML, the total leukocyte count usually ranges from 50 × 10^9/L at the time of diagnosis and can extend up to 800 × 10^9/L. Also, a subset of patients may present with mild increase in WBC count and a marked increase in the platelet count.
2. The **peripheral blood smear** shows a full spectrum of myeloid cells from blasts to neutrophils, with blasts comprising less than 10% and usually less than 5% of the WBC differential (Fig. 4). Basophilia is invariably present, and its absence should prompt consideration of other myeloproliferative disorders. Eosinophilia is also commonly present.
3. The **bone marrow** is hypercellular, with a myeloid preponderance (Fig. 5). Blasts percentage depends on the phase of the disease, and basophilia is present. Megakaryocytes are usually increased in number and are characteristically small, hypo- or monolobated, with a tendency to cluster. Erythroid precursors are morphologically unremarkable. Reticulin fibrosis is usually absent or mild and correlates with splenic enlargement. It may become more prominent with disease progression.
4. ***Cytogenetics***: Fluorescent in situ hybridisation (FISH) is a rapid and sensitive test for diagnosis and the standard method to detect philadelphia (Ph) chromosome, which is present in the majority of cells at diagnosis. Although t(9;22)(q34;q11) is common in most patients, approximately 5% have variant translocations that have no impact on prognosis. Additional clonal cytogenetic abnormalities such as duplication of the Ph chromosome, trisomy 8, iso-17q, and trisomy 19 and deletion 7q/7-are present in 5% of cases. Presence of deletion 7q/7-indicates accelerated phase and can be a marker of coexistent myelodysplastic syndrome.

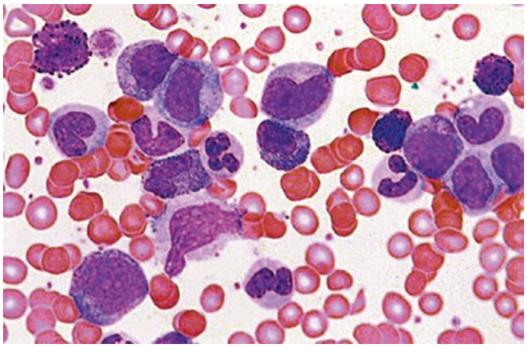

Fig. 4 Peripheral smear of CML

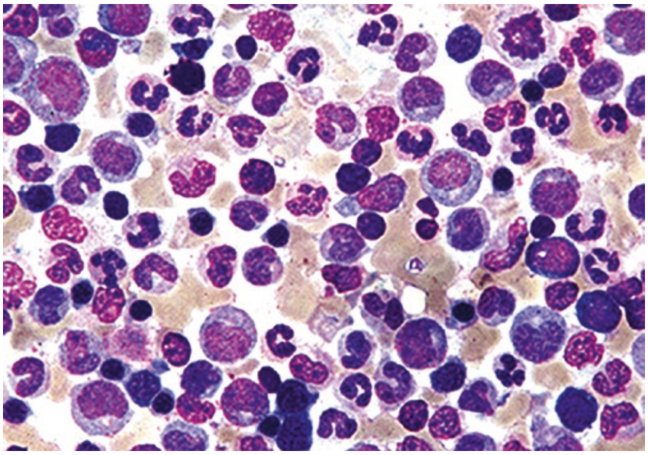

Fig. 5 Bone marrow appearance in CML

Conventional karyotype can be used for diagnosis and to define complete cytogenetic response.

4.4.2 Molecular Tests

Qualitative reverse transcriptase polymerase chain reaction is used to detect and identify the transcript of BCR-ABL (p210 in 90% cases and rarely p190 and p230).

Quantitative PCR is used to follow the molecular response at certain time points.

4.4.3 Prognostic Factors

For treatment-naive CP patients, three risk scores are utilised: Sokal, Euro and EUTOS. The latest addition to prognostic score is ELTS (Eutos long-term survival) score. Other than these scores, presence of fibrosis in the bone marrow biopsy and additional chromosomal abnormalities is considered as high-risk factors for progression and lesser response to TKIs.

4.5 Treatment at TMH

First line treatment options: CML-CP

- Imatinib 400 mg OD
- Dasatinib 100 mg OD
- Nilotinib 300 mg BD

4.6 Practical Management Algorithmwfor CML

The goals of treatment are defined in Table 6.

4.7 Monitoring of CML

1. Complete blood counts: To be monitored once in 2 weeks until achievement of a CHR and then at 1–3 monthly intervals.
2. Cytogenetics: Monitored at 6 months and repeated at 12 months if not in CCYR.
3. Molecular studies: PCR for Bcr Abl should be repeated at 3-monthly intervals, the frequency can be reduced to once in 6 months after MMR is attained (Table 7).
4. Tyrosine kinase domain mutation studies: TKD mutation studies are performed in those who have treatment failure, or present with accelerated/blast phase.

Table 6 Definition of the response to TKIs (any TKI) as first-line treatment

	Optimal	Warning	Failure
Baseline	NA	High risk or CCA/Ph+, major route	NA
3 months	BCR-ABL1 ≤10% and/or Ph+ ≤35%	BCR-ABL1 >10% and/or Ph+ 36–95%	Non-CHR and/or Ph+ >95%
6 months	BCR-ABL1 <1% and/or Ph+ 0	BCR-ABL1 1–10% and/or Ph+ 1–35%	BCR-ABL1 >10% and/or Ph+ >35%
12 months	BCR-ABL1 ≤0.1%	BCR-ABL1 >0.1–1%	BCR-ABL1 >1% and/or Ph+ >0
Then, and at any time	BCR-ABL1 ≤0.1%	CCA/Ph− (−7, or 7q−)	Loss of CHR
			Loss of CCyR
			Confirmed loss of MMR[a]
			Mutations
			CCA/Ph+

[a] PCR >0.1%

Reference: A. Hochhaus, Leukemia (2020)

Table 7 Treatment options based on the BCR-ABL kinase domain mutation status

Mutation	Treatment recommendation
T315I	HSCT/clinical trial
V299L, T315A, F317L/V/I/C	Consider Nilotinib than Dasatinib
Y253H, E255K/V, F359V/C/I	Consider Dasatinib than Nilotinib
Any other mutation	Consider high dose Imatinib or Dasatinib or Nilotinib

Reference: A. Hochhaus, Leukemia (2020)

4.8 Treatment-Free Remission

Discontinuation of TKI can be considered if following requirements are fulfilled:

- Mandatory:
  - In CML-CP only
  - Motivated patient with
  - Access to high quality qPCR with International scale
  - Turnaround time of PCR results <4 weeks
  - Patient's agreement to more frequent monitoring after stopping TKIs (monthly for first 6 months, every 2 months for 6-12 months, every 3 months thereafter
- Minimal:
  - First line therapy or second line if intolerance was the only reason for change on TKI
  - Typical e13a2 or e14a2 BCR-ABL transcripts
  - Duration of TKI therapy for >5 years (>4 years for 2GTKI)
  - Duration of deep MR (MR^4 or better) >2 years
  - No prior treatment failure

Studies that tested the concept of TFR:

1. STIM-1 (Stop Imatinib study)
2. A-STIM
3. Euro-SKI

5 Chronic Lymphocytic Leukemia

CLL is a clinically heterogeneous disease originating from B lymphocytes that may differ in activation, maturation state, or cellular subgroup. Only patients with advanced or symptomatic disease require treatment. Some patients remain indolent with no need for treatment. The 5-year survival for patients with CLL is 55–83%, however it mainly depends on the stage.

5.1 Incidence and Epidemiology in India and Global

CLL is the most common leukaemia in the Western world with an annual incidence of 4.2 patients per 100,000 person population. It comprises 25% of all leukaemia as compared to 1.7–8.8% of all leukaemia in the Indian population. CLL is common in the elderly with a median age of 72 years at diagnosis. The male to female ratio is 2:1. Also, family members of CLL patients have an inherited genetic susceptibility of six- to nine-fold for CLL.

5.2 Clinical Presentation in India and Global

Around 25–50% patients in the west are incidentally diagnosed as compared to 20% of patients in Indian population. Lymphadenopathy is the most common presenting symptom, seen in 87% of patients at the time of diagnosis. Advanced disease with anaemia and thrombocytopenia are present at the time of initial presentation in 20% of cases, and up to 20% of cases present with B symptoms (fever, night sweats and weight loss). Also, 10% of patients may initially present with hepatomegaly and splenomegaly. Autoimmune haemolytic anaemia is present in 10% of patients.

5.3 Evaluation and Work-Up

Clinical history—duration of symptoms, presence or absence of B symptoms, presence of nodal swelling, symptoms of anemia, thrombocytopenia, compressive symptoms due to massive spleen or nodal swelling.

Physical exam with attention to pallor, node-bearing areas, including Waldeyer's ring, and to size of liver and spleen.

Determination of performance status.

5.4 Work-Up for Confirmation of Diagnosis

- Complete blood count and peripheral smear—Diagnosis of CLL requires the presence of $\geq 5 \times 10^9$/L clonal B lymphocytes in the peripheral blood. Peripheral smear demonstrates small, mature-appearing lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin. This is accompanied by a small percent of prolymphocytes that are larger cells with more cytoplasm and prominent central nucleoli. It usually shows the presence of smudge cells, which are artefacts from lymphocytes damaged during slide preparation.
- Immunophenotyping—Clonality of the circulating B lymphocytes should be confirmed by flow cytometry. The presence of cell surface markers with dim kappa/lambda, CD19, dim CD20, CD5, variable CD23, and CD200.
- FISH—Cytogenetic abnormalities, in particular a deletion of chromosome 17 [del(17p)], 13[del(13q)] and 11[del(11q)] and trisomy of chromosome 12. These have prognostic and predictive value.
- Molecular analysis to detect *IGHV* mutation status, determination of CD38 and ZAP-70 expression by flow cytometry or immunohistochemistry, TP53 sequencing.
- Bone marrow aspiration and biopsy—Indicated to evaluate for the cause of unexplained cytopenias—autoimmune and myelodysplastic causes.
- Lymph node biopsy—indicated to rule out Richter's transformation.

5.5 Principles of Management

Treatmentoptions for chronic lymphocytic leukemia (CLL) have evolved overthe last several years. The two commonly followed staging systems are the Rai system and Binet system. Generally, patients in the early-stage CLL should not be treated with chemotherapy until they become symptomatic or display evidence of rapid progression of disease. Patients at low and intermediate risk (i.e. Rai stages 0-II) who have no indications for treatment should be observed. Blood cell counts and clinical examinations should be performed every 3–6 months.

5.6 Medical Management and Monitoring

Indications for treatment include the following:

- Presence of B symptoms
- Extreme fatigue (performance score >2)

- Progressive marrow failure (anaemia or thrombocytopenia)
- Autoimmune anemia or thrombocytopenia not responding to glucocorticoids
- Progressive or symptomatic splenomegaly
- Massive or symptomatic lymphadenopathy
- Progressive lymphocytosis, as defined by an increase of >50% in 2 months or a doubling time of less than 6 months

Along with disease-specific measures, complications like tumour lysis syndrome, immune mediated cytopenias, recurrent infections and risk of secondary malignancy should also be addressed. Pneumococcal and influenza vaccines are recommended. Corticosteroids, usually prednisoloneat a dose of 1 mg/kg/day daily initially, followed by gradual dose tapering, may be useful in patients with AIHA. Rituximab, alone or as part of a combination regimen, can be very effective in eliminating the B-cell clone that induces autoimmune disorders, particularly for patients with autoimmune thrombocytopenia.

Therapy recommendations for patients at high risk (i.e. Rai stages III–IV) and progressive cytopenia are based on the following:

- Patient age
- Patient comorbidities
- Presence or absence of del(17p) and IgVH mutation

Treatment options for CLL patients with IgVH mutated status, in the absence of 17p deletion are as follows:

- Patients <65 years, glomerular filtration rate (GFR) >70 mL/min and without significant comorbidities (CIRS Cumulative Illness Rating Scale <6: FCR (fludarabine, cyclophosphamide, rituximab))
- Patients ≥65 years and younger patients with significant comorbidities: Bendamustine + Rituximab (B + R), Ibrutinib, Obinutuzumab plus Chlorambucil.

CLL patients with del(17p) have a poor prognosis and there is no clear standard of care. The treatment options include

- Ibrutinib (ORR 97%, 2 years OS 84%)
- Allogenic stem cell transplant

CLL patients with IGHV unmutated status:

- IGVH unmutated: Ibrutinib is preferred in all patients.

Disease response should be done by clinical examination, blood count monitoring and CT scan or USG Abdomen, CXR after 3 months of therapy.

Minimal residual disease (MRD at <0.01%) at the end of therapy can be used as a prognostic tool to predict time to next therapy and OS.

5.7 Management Algorithm According to Risk Stratification (Fig. 6)

Prognosis

CLL International prognostic score: prognostic factors	Points
Del 17p or TP53 mutation	4
Unmutated IGVH status	2
Serum beta 2 microglobulin >3.5 mg/L	2
Rai stage I–IV	1
Age >65 years	1

IPI score	Risk	5-year TFS
0–1	Low risk	78%
2–3	Intermediate	54%
4–6	High	32%
7–10	Very high	0%

5.8 Management of Recurrent Disease Including Specific Palliative Measures

Historically, chemoimmunotherapy had been the standard of care for patients with relapsed/refractory CLL. This rapidly changed a few years ago with the introduction of targeted therapies. Treatment for relapsed disease depends on the status of 17p deletion, treatment free interval, age, comorbidities and response and tolerance to previous treatment. Ibrutinib is the preferred drug for patients with relapsed disease if not given upfront. Other drugs that can be used in relapsed/refractory disease include venetoclax plus rituximab, idelalisib, acalabrutinib, chlorambucil with or without rituximab, lenalidomide with or without rituximab and alemtuzumab with or without rituximab. European guidelines recommend allogeneic stem cell transplantation in patients with high-risk *p53* mutation and/or refractory disease to small molecule inhibitor therapy. Richter's transformation to DLBCL is generally managed with chemoimmunotherapy recommended for DLBCL and is associated with poor prognosis. Chimeric antigen receptor therapy (anti CD-19) is under development for relapse/refractory CLL.

5.9 How We Do It at TMC

Patients without 17p deletion are generally treatment with FCR or BR regimen depending on age and comorbidities. Since the generic brand of Ibrutinib is now available in India, at a very low cost compared to the original molecule, patients

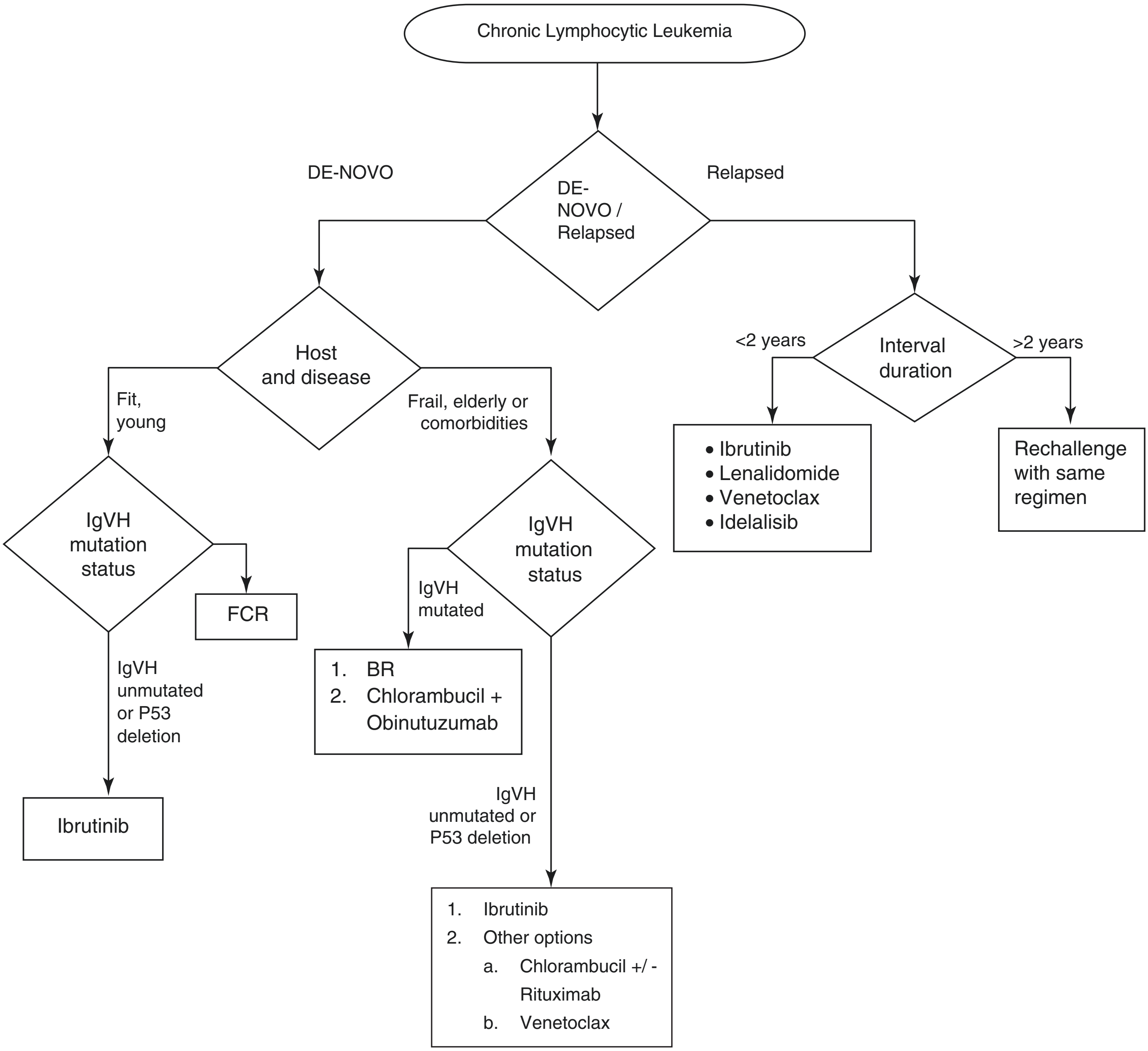
Chronic Lymphocytic Leukemia
DE-NOVO
Relapsed
DE-NOVO / Relapsed
Host and disease
Fit, young
Frail, elderly or comorbidities
Interval duration
<2 years
>2 years
• Ibrutinib
• Lenalidomide
• Venetoclax
• Idelalisib
Rechallenge with same regimen
IgVH mutation status
FCR
IgVH unmutated or P53 deletion
Ibrutinib
IgVH mutation status
IgVH mutated
1. BR
2. Chlorambucil + Obinutuzumab
IgVH unmutated or P53 deletion
1. Ibrutinib
2. Other options
a. Chlorambucil +/- Rituximab
b. Venetoclax

Fig. 6 Management algorithm for CLL according to risk stratification

with 17p deletion or IGVH unmutated status are treated with Ibrutinib. Treatment of relapsed patients is individualised depending on age, comorbidities, performance status, disease-free interval and logistics.

6 Hairy Cell Leukemia

Hairy cell leukemia (HCL) is a rare variety of mature B cell lymphoproliferative disorder characterized by and named after typical cells seen in peripheral smear. Cell of origin seems to be post germinal memory B cells or possibly splenic marginal zone B cells.

6.1 Incidence and Epidemiology in India and Global

Hairy cell leukemia is uncommon. Its incidence in India is not known. In United States, it accounts for about 1000 cases per year. It is about 4–5 times more common in men than in women.

6.2 Clinical Presentation in India and Globally

Patient presents with pancytopenia or its complications (fever, fatigue andbleeding) and/or splenomegaly (left upper quadrant abdominal pain). Lymphadenopathy is rare and involves the retroperitoneal nodes.

6.3 Evaluation and Work-Up Including Risk Stratification

Complete blood count with peripheral smear (pancytopenia, hairy projections bearing leukemic cells), immunophenotyping (CD19, CD20, CD11c, CD25, CD200, CD103, CD123 and annexin A1), bone marrow studies (aspiration: dry tap and biopsy), viral markers, chest X-ray or CT scan thorax to look for infection. There is specific score to differentiate HCL from HCL-variant and splenic diffuse red pulp small B cell lymphoma. It is very important to differentiate these entities because prognosis and treatment changes with diagnosis. BRAF V600E mutations are seen in almost all patients.

Spleen size, absolute hairy cell count, leucocytosis, beta-2 microglobulin level and IGHV mutation are various factors having prognostic implications.

6.4 Principles of Management (an Integrated Brief Overview of Rx Philosophy)

Treatment is indicated when cytopenias develop or when symptomatic (organomegaly, lymphadenopathy and B symptoms). Asymptomatic patients can be kept under watch and wait strategy.

Purine analogues is the treatment of choice in first line for all HCL patients. Infections should be treated prior to start of purine analogues.

Based on the time to relapse, various strategies are used for attaining remission. Options are to rechallenge with same or other purine analogue, purine analogue with rituximab, BRAF inhibitors, antiCD22 drug conjugate.

6.5 Medical Management and Monitoring

Pentostatin and cladribine in various schedule are drug of choice for first-line treatment. Interferon alpha, low-dose pentostatin or BRAF inhibitors may be used in pregnant female or in case where infection control is difficult. Pentostatin and cladribine are never compared but seems both are equally efficacious. In our setup, generally cladribine is preferred.

Cladribine: 0.1 mg/kg as IV infusion for 7 days
0.14 mg/kg IV over 2 h for 5 days
Pentostatin: 4 mg/m^2 every 2 weeks

Response should be assessed by haematological parameters, physical examination and bone marrow evaluation. CBC should be monitored serially post treatment for count recovery. Bone marrow should be evaluated after about 6 months if cladribine is used or after achievement of clinical response if pentostatin is used. MRD with 8 colour flow cytometry can be helpful to predict long-term remissions.

Some investigators believe in giving consolidation with Rituximab after initial induction with purine analogues.

6.6 Prognosis with Current Rx

Most patients (>90%) can achieve durable long-term remission. Though treatment is not curative, but it can prolong survival to near normal lifespan. Median PFS with purine analogues is 9–11 years.

6.7 Management of Recurrent Disease Including Specific Palliative Measures

Some patients will have stable disease (4%) or PR (20%). Rechallenge with other purine analogue is an option for them. Those who do not respond to two lines of purine analogues alternative treatment options like anti CD22 (moxetumomab pasudotox-tdfk), BRAF inhibitors (vemurofenib), bendamustine plus rituximab, single-agent rituximab, interferon alpha, splenectomy or other investigational therapies.

Treatment for relapse patient depends on time to relapse. For patients who relapse after more than 5 years, the same purine analogue should be rechallenged or another nucleoside analogue can be used. For those who relapsed between 2 and 5 years, purine analogue plus rituximab should be used. For those who relapsed before 2 years one should confirm the diagnosis and if confirmed than one should use alternative options like anti CD22 (moxetumomab pasudotox-tdfk), BRAF inhibitors (vemurafenib), bendamustine plus rituximab, single-agent rituximab, interferon alpha, splenectomy or other investigational therapies.

Splenectomy is used sometimes in very symptomatic patient or in pregnant patient for palliative measure.

6.8 How We Do It at TMC

We manage HCL patients with single-agent cladarabine 0.1 mg/kg IV infusion for 7 days along with supportive care including antibacterials, antifungal in first line. We observe patients after induction and do bone marrow for response evaluation at about 6 months. Relapsed and resistant patients are treated on a case-by-case basis based mainly on time to relapse.

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Adult Lymphomas

Manju Sengar and Sumeet Gujral

Abbreviations

BMB	Bone marrow biopsy
CNS	Central nervous system
DLBCL	Diffuse large B-cell lymphoma
EBV	Epstein–Barr virus
ESMO	European Society for Medical Oncology
FDG	Fluorodeoxyglucose
FISH	Fluorescent in-situ hybridization
GHSG	German Hodgkin Study Group
HL	Hodgkin lymphoma
LP	Lymphocyte predominance
NHL	Non-Hodgkin lymphoma
NS	Nodular sclerosis
PCR	Polymerase chain reaction
PET	Positron emission tomography
TCR	T-cell receptor

1 Introduction

The term “lymphomas” comprises of biologically and clinically heterogeneous group of neoplasms that are derived from the cells of lymphoid lineage. Conventionally, they have been divided into non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). There has been significant progress in understanding of the biology and therapeutics of lymphomas over the past few decades. The molecular characterization and various genetic abnormalities associated with the development of lymphomas has led to the notion of lymphomas being clonal expansion of B and T lymphocytes. Hodgkin lymphoma is a B-cell malignancy characterized by the presence of large atypical cells—the Hodgkin–Reed–Sternberg (HRS) cells scattered in a complex inflammatory stroma [1]. Biology, treatment and outcomes vary based on the subtype of Hodgkin and non-Hodgkin lymphomas [2].

2 Incidence and Epidemiology

Non-Hodgkin lymphoma (NHL) is a common hematological malignancy. They comprise a heterogeneous group of disorders and account up to 3–5% of all malignancies. According to Globocan (2018), the estimated incidence of NHL is 6.6/100,000 (509,590 new cases), with a mortality rate of 2.6% of all cancer-related deaths (248,724 deaths) worldwide [3]. The estimated incidence of HL is 1.03/100,000 with a mortality rate of 0.3% of all cancer-related deaths worldwide. The age-adjusted incidence rates for NHL in men and women in India are 2.9/100,000 and 1.5/100,000, respectively [4]. The incidence is significantly lower than Western countries. The variation in incidence between urban and rural cancer registries within India suggest potential role of urbanization and lifestyle changes. There is a variability in the frequency of various subtypes of NHL in India as compared to Western countries. Diffuse large B-cell lymphoma is the commonest subtype followed by follicular lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia, mantle cell lymphoma and marginal zone lymphoma. The prevalence of T-cell lymphoma is higher than the western countries but lower than the other Asian countries. Among the T-cell lymphomas, T-cell lymphoblastic lymphoma, anaplastic large cell lymphoma and other nodal peripheral T-cell lymphomas account for 6%, 4.3% and 2.9% of all cases, respectively. The median age of diagnosis varies based on the subtype of lymphoma [5, 6].

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The age of onset of HL reveals a bimodal distribution with a first peak in the third decade and a second peak after the age of 50. It affects men more commonly age compared to women [7].

Several risk factors for development of non-Hodgkin lymphoma have been evaluated. These include immune deficiency, autoimmune disorders, infections, environmental factors, genetic predisposition and obesity [8]. Genome-wide association studies have identified loci that are associated with increased for follicular lymphoma, marginal zone lymphoma and DLBCL. Autoimmune diseases including rheumatoid arthritis, Sjogren syndrome and systemic lupus erythematosus contribute to the development of NHL through underlying altered immune dysregulation and immunosuppressive therapy. Patients with primary or secondary immunodeficiency (organ transplantation and HIV/AIDS are at an increased risk of developing NHL. Infections, like *Helicobacter pylori* (gastric mucosa-associated lymphoid tissue), Epstein–Barr virus (Burkitt lymphoma and NK–T-cell lymphoma) and Hepatitis C virus (splenic marginal zone lymphoma) have shown to be causative for certain specific subtype [9–11].

The etiology of HL is not well understood. Epstein–Barr virus (EBV) and immunodeficiency have shown to increase the risk [12, 13].

3 Clinical Features and Staging of Lymphomas

The most common presentation of patients with NHL is painless lymphadenopathy, with or without constitutional symptoms such as fever, nights' sweats, weight loss and fatigue. In HL patients may present with relatively long-standing duration of painless lymphadenopathy. The most common sites of disease presentation—cervical, mediastinal and/or abdominal nodal enlargement. Symptoms vary based on the site of involvement. Superior vena cava obstruction, cough, shortness of breath can occur due to mediastinal lymphadenopathy. Abdominal lymphadenopathy can present as abdominal pain or obstructive symptoms. Similarly, extranodal site of involvement can present as mass or organ specific symptoms. Pruritus with or without skin lesions indicate the possibility of HL.

The Ann Arbor staging system was first developed for staging of HL and later was used for NHL too [14]. The Ann Arbor staging system divides patients into four stages based on nodal site location, number of nodal areas, presence and extent of extranodal sites, liver and bone marrow involvement (Table 1). The staging system has evolved over the years and now with the use of PET-CT, Lugano staging criteria are used for both HL and NHL which are FDG (fluorodeoxyglucose) avid (Table 2).

Table 1 Ann Arbor classification and the Cotswold modifications

Stage	Features
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extranodal site(s) beyond that designated E
For all stages	
A	No symptoms
B	Fever (>38 °C), drenching sweats, weight loss (10% body weight over 6 months)
For stages I to III	
E	Involvement of a single, extranodal site contiguous or proximal to known nodal site
Cotswold modifications	Massive mediastinal disease has been defined by the Cotswold meeting as a thoracic ratio of maximum transverse mass diameter greater than or equal to 33% of the internal transverse thoracic diameter measured at the T5/6 intervertebral disc level on chest radiography. The number of anatomic regions involved should be indicated by a subscript (e.g., II3) Stage III may be subdivided into: III1, with or without plenic, hilar, celiac or portal nodes; III2, with para-aortic, iliac, mesenteric nodes Staging should be identified as clinical stage (CS) or pathologic stage (PS) A new category of response to therapy, unconfirmed/uncertain complete remission (CR) can be introduced because of the persistent radiologic abnormalities of uncertain significance

Table 2 Revised staging system for primary nodal lymphomas

Stage	Involvement	Extranodal (E) status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky[a]	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography-computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue

[a] Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors

4 Evaluation and Work-Up of Lymphomas

4.1 Lymphoma Diagnosis: Lab Approach

4.1.1 Morphological/Histopathological Approach to Lymphoma Diagnosis

Lymphoma diagnosis is based on an adequate and representative biopsy sample to be reviewed by a hematopathologist. It is preferable to have an excisional biopsy of the largest palpable lymph node or of the lesion in the extranodal site. Sometimes incisional or core biopsy is the only feasible option. Diagnosis based only on morphology of a fine-needle aspiration cytology or an effusion should be avoided unless until it is supplemented with ancillary techniques like flow cytometry or molecular diagnostics. Morphological mimics of various subtypes of lymphoma are many, and differential diagnosis varies for each specific morphological subtype.

Optimal fixation and processing of tissue is mandatory for morphological as well as immunophenotypic interpretation. A good quality H&E section is a key to lymphoma diagnosis. It is important to have a low power lens in the microscope, preferably 1× (expensive) or else a 2× lens.

4.1.2 Immunophenotyping

IHC is routinely available in most surgical pathology laboratories and help in work up of hematolymphoid neoplasms. There are more than 250 CD markers available today and approximately 40–45 being routinely used in IHC labs for diagnosis of HLN (Table 3). It is important to understand reactions of these markers with respect to normal cells in the lymphoid and other organs. An example is of Bcl-2 reaction in a normal lymph node. Bcl-2 is commonly used in the differential diagnosis of follicular lymphoma from follicular hyperplasia. In a normal node Bcl-2 is expressed by mantle cells, marginal zone cells, interfollicular T cells and in follicular T helper cells (CD4+) present within the germinal centers. Similarly, Pax5 is a B-cell transcription factor with strongest expression in mantle zone cells, weak to moderate in germinal center B cells, weak in RS cells (in CHL) and negative in plasma cells and T cells. CD138 is a marker for plasma cells and is also expressed in epithelial cells. CD10 is a marker used in hematolymphoid neoplasms where it is expressed in precursor B-cell ALL, DLBCL, FL, BL, AITL and also in benign lymphoid cells like hematogones and also in neutrophils and stromal cells. CD10 expression in neutrophils is used as an internal control in FCI.

4.1.3 Cytogenetics

Cytogenetics has an equally important role in diagnosis and prognostication of various lymphomas. Interphase fluorescent in-situ hybridization (FISH) is performed in lymphomas as it is difficult to get adequate mitoses in lymphoma cells. FISH analysis can be performed on peripheral blood, bone marrow aspirate, fluids or cytology smears, lymph node paraffin sections, etc. The panel for FISH is mainly dependent on the final tissue diagnosis. Specific chromosome abnormalities are strongly associated with particular subtypes of lymphomas, e.g., t(8;14) or variants in Burkitt lymphoma and t(11;14) in Mantle cell lymphoma, etc.

Table 3 Immunohistochemistry for diagnosis of lymphomas

Essential markers for a hematopathology laboratory
LCA, CD20, CD3, CD5, CD23, CyclinD1, Mib1, CD10, bcl6, bcl2, CD43, CD15, CD30, Alk1, Pax5, Tdt, CD34, CD138, MPO, Mum1, CKIT, EBVLMP1/EBER (ISH)
Comprehensive panel of antibodies as a lymphoma panel
B-cell lymphoma panels: CD20, CD79a, CD19, CD23, CD10, MYC, CD5, BCL2, BCL6, Ki67, IRF4/Mum1, CD21, CD23, CD35, Cyclin D1, Pax5, Tdt, CD138, kappa and lambda light chains, CD43, p21, Annexin A1, CD123
Hodgkin lymphoma panel: LCA, CD3, CD20, CD15, CD30, Pax5, ALK1, IRF4/Mum1, EBV-LMP1, EBE-EBER (ISH), Oct2, Bob1, EMA, CD57
T/NK cell lymphoma panel: CD2, CD3, CD4, CD5, CD7, CD8, CD56, Ki67, CD23, CD10, CD25, CD30, Alk1, Tdt, CD56, CD57, Perforin, Granzyme, TIA-1, PD1, CD123
Miscellaneous: C-kit, MPO, CD33, HLADR, CD1a, CD163, CD61/CD41, CD235, CD71, etc.
Other markers: CK, EMA, S-100, HMB45, Melan A, Desmin, Mic2, FLI1, MyoD1, Myogenin, Synaptophysin, Chromogranin, ER, PR, Cerb b2
Different lymphoma subtypes and panels
DLBCL: CD10, bcl6, Mum1, Mib1, bcl2, MYC
Plasma cell neoplasms: CD79a, CD38, CD138, kappa/lambda light chains, CD56, EMA, Mum1, cyclinD1, CD19, C-kit
Small cell lymphomas: CD5, CD23, CyclinD1, bcl-6, CD10, CD43, bcl2
Burkitt lymphoma: bcl2, MiB1, CD10
Lymphoblastic lymphoma: CD3, CD99, TdT, Pax5, CD79a, CD10, CD4, CD8 (for B-LL, CD79a and CD19 are better markers as the blasts might be negative for LCA and CD20)
Granulocytic sarcoma: CD43, MPO, cKit, CD34
ALCL: CD30, ALK-1, EMA, CD3, CD4, CD8, CD20
PTCL/AITL: CD3, CD2, CD5, CD7, CD56, CD30, ALK1, CD23, CD10, CD4, CD8, PD1, Tdt
Suspected NK cell lymphoma: CD3, CD56, CD57, EBER (Others: CD8, TIA-1, granzyme B)
Histiocytic differentiation: PGM1 (CD68), CD163, CD1a
Dendritic cell: CD21, CD23, CD35, S-100
Classical HL: LCA, CD3, CD20, Pax5, CD15, CD30, Alk1, EBER ISH, EBV LMP1
NLPHL: CD20, CD3, CD56, Oct2, Bob1, CD23, CD30, EBER, EBVLPM1
Cutaneous lymphomas: CD3, CD20, CD4, CD8, CD5, CD7, CD10, CD30, BCL2
EBV-related lymphomas: EBER by in-situ hybridization

4.1.4 Molecular Tests

T and B lymphoid cells are involved in immune function for the recognition of foreign antigens by the specificity of their surface T-cell receptor (TCR) and immunoglobulin, produced by gene rearrangement. Each T and B lymphocyte carries a unique arrangement of TCR or immunoglobulin genes, which helps in identification of clonality of mature T- and B-cell proliferations. IGH and TCR gene rearrangement by polymerase chain reaction (PCR) can be performed on any sample, i.e., peripheral blood, bone marrow aspirate or paraffin-embedded tissues (lymph node or bone marrow biopsy). Molecular studies are important for diagnosis, as well as for detection of minimal residual disease. While the use of PCR for specific translocations such as t(14:18) and for detection of T-cell and B-cell clonality based on TCR and Ig heavy and light chain gene rearrangement studies is an important diagnostic test, false positives and negatives are not uncommon; therefore, PCR results should not form the sole basis for diagnosis. Diagnosis of hematolymphoid neoplasms is based on a multidisciplinary approach.

The **staging work-up** includes a detailed history taking and physical examination; laboratory studies to assess the organ function, serum lactate dehydrogenase; and imaging studies.

For HL FDG-avid NHL subtypes, PET-CT improves the accuracy of staging compared with CT and tends to upstage in 10–20% of patients. In majority of cases, the upstaging does not alter the management and may not have impact on the overall survival. It helps in improving staging accuracy ensures that fewer patients are undertreated or overtreated [15, 16].

Bone marrow biopsy (BMB) is an important component of staging in NHL. Patients who demonstrate bone marrow involvement on PET-CT need not undergo a bone marrow examination unless the discordant histology is being suspected. The negative predictive value of PET-CT in NHL is not as good as HL. In patients with HL, BMB is not required if a staging PET-CT is done [17]. In diffuse large B-cell lymphoma (DLBCL), PET-CT is more sensitive than BMB but has been reported to miss low-volume diffuse involvement of 10–20% of the marrow [18]. In all other lymphoma subtypes a 2.5-cm long unilateral BMB and aspiration is recommended, subjected for immunohistochemistry and for flow cytometry.

Several systems for predicting prognosis or prognostic indices have been developed for different lymphoma subtypes. The value of these indices is dependent on the treatment being offered. n. International prognostic index for aggressive B-cell lymphoma has been modified over the years to delineate its role based on the age, stage and use of rituximab [19]. Modification of the IPI for DLBCL seems to improve its predictive value. Other systems exist, sometimes with several iterations, for follicular lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma and NK–T-cell lymphoma [20–23].

5 Principles of Management of Lymphomas

Lymphomas are essentially curable malignancies. Apart from asymptomatic low grade/indolent lymphomas which may be managed by a wait and watch policy, majority of the lymphomas merit treatment with chemotherapy. Systemic therapy remains the primary modality of treatment for majority of HL and NHL. The selection of drugs, regimen and duration is decided based on the subtype and stage of the disease.

The role of surgery is limited to the initial diagnostic workup (excisional and incisional biopsy) or for management of oncological emergencies like acute abdomen and cord compression. Critically important in the diagnosis and staging process but recently has had limited importance. Radiotherapy is used in combination with chemotherapy as consolidation or to address the residual disease or as part of combined modality therapy. In low-grade lymphomas with limited stage disease radiotherapy can be the only modality of treatment.

Supportive care has a pivotal role in the management of lymphomas. It is required during the entire continuum of treatment. High-tumor burden, tumor lysis syndrome, superior vana cava syndrome, massive pleural effusion, pericardial effusion, acute abdomen, cord compression and renal dysfunction due to obstructive uropathy will need urgent attention to enable the delivery of definitive treatment. During therapy, management of nausea and vomiting, mucositis, febrile neutropenia and other treatment-related side effects are crucial to reduce the morbidity, treatment compliance and mortality.

6 Management of Non-Hodgkin Lymphomas

6.1 Precursor B- and T-Cell Lymphomas

Lymphoblastic lymphoma (LBL) can be of pre-B-cell or pre-T-cell origin and is evaluated and treated on similar lines as acute lymphoblastic leukemia (ALL). The clinical presentation includes mediastinal mass in T-LBL, whereas skin, bone and nodal involvement are common in B-LBL. T-LBL presents at younger age as compared to B-LBL. LBL tends to involve central nervous system like ALL, and therefore, a baseline cerebrospinal fluid (CSF) examination is mandatory. The treatment is based on pediatric inspired ALL regimen in patients who are fit. Use of prophylaxis for CNS is mandatory. Mediastinal radiation is used in patient treated with adult protocols. Like ALL, maintenance therapy is essential component of treatment [24].

6.2 Mature B-Cell Lymphomas

6.2.1 Diffuse Large B-Cell Lymphoma (DLBCL)

DLBCL is the most common subtype of non-Hodgkin lymphoma. Chemoimmunotherapy with R CHOP (rituximab plus Cyclophosphamide doxorubicin vincristine and prednisolone) remains the cornerstone for management of DLBCL and led to a significant improvement of outcomes [25].

Based on the cell of origin, DLBCL is divided into two subtypes—germinal center type (GCB) and activated B-cell type (ABC). The GCB type have a better prognosis than ABC type. Though rituximab has led to significant improvement in outcomes of both the subtypes, it does not overcome the negative prognostic effect of the activated subtype [26].

Patients with early stage DLBCL have an excellent outcome with the long-term survival close to 80–90%. Abbreviated chemotherapy with radiotherapy can be employed, but chemoimmunotherapy alone can cure most patients [27]. In the rituximab era, the role of radiotherapy in patients with negative PET-CT after the chemoimmunotherapy is questionable.

Lymphomas with mutations/gene rearrangements involving both MYC and either Bcl-2 or Bcl-6 genes have been referred to as double-hit lymphomas. They exhibit features intermediate between DLBCL and Burkitt lymphoma. DLBCLs with MYC and Bcl-2 mutations are of germinal center B-cell origin, and those with MYC and Bcl-6 are often of activated B-cell origin [28]. Double-hit lymphomas respond poorly to the standard R CHOP, have a lower incidence of complete remission and increased likelihood of primary progression on therapy. The risk of CNS relapse is also high. Many attempts to improve the outcome of patients with the double-hit subtype type of DLBCL have been studied. Infusional EPOCH-R regimen with CNS prophylaxis (commonly with intrathecal methotrexate) is one such development but with limited success. Lymphomas that overexpress the proteins Bcl-2 and MYC but do not have translocations in the respective genes have been referred to as double expressors: usually of activated B-cell origin and have a poor outcome. However, the outcome is intermediate between double-hit DLBCLs and DLBCLs that are neither double-hit nor double expressors.

The risk of CNS relapse in patients with advanced DLBCL is about 5% and reaches to nearly 15–20% for patients with high IPI score. Chemoimmunotherapy alone does not reduce the risk of CNS relapse. Specific extranodal sites such as testes, orbit, kidneys, adrenal, breast, paranasal sinuses, paravertebral masses and marrow are more frequently associated with CNS involvement. Patients with high IPI score, high-levels of LDH and involvement of more than one extranodal site are at much higher risk of CNS relapse. Hence, in these patients, incorporation of CNS prophylaxis either in the form of intrathecal methotrexate or high-dose methotrexate is beneficial.

DLBCL subtypes arising in extranodal sites can have unique clinical features. Primary mediastinal B-cell lymphoma is seen more often in young women and it has tendency to spread to other extranodal sites [29]. With CHOP-R alone the outcomes are inferior when compared to intensive alkylator-based protocols like MACOP-B or HperCVAD. However, toxicities preclude the usage of these regimens commonly. In one study of EPOCH-R without radiotherapy, event-free survival was reported to be 93%. A negative PET-CT at the end of chemotherapy facilitates the omission of mediastinal radiation and thus spare the patients of its long-term toxicities [30].

In case RCHOP is used, a combination with radiotherapy is mostly required.

Primary CNS lymphoma can be cured by chemotherapy regimens that include high-dose methotrexate and/or high-dose cytarabine during the induction. Consolidation with high-dose chemotherapy and autologous stem cell transplant is a viable option in suitable patients. Given its long-term side effects, especially neurocognitive and behavioral, cranial irradiation, is not primarily used for consolidation unless residual disease persists post induction [31].

6.2.2 Burkitt Lymphoma

Burkitt lymphoma is the most rapidly proliferating human malignancy (doubling time of 24–48 h), and because the disease can progress so rapidly and has a tendency to disseminate to the CNS, a timely diagnosis and prompt institution of effective therapy are important. Staging must be completed rapidly in order to avoid delay of therapy, which must start within 48 h after diagnosis.

CNS directed prophylactic therapy must be included and is the backbone in any treatment protocol employed for Burkitt lymphoma. Very intensive, short-course, multiagent, noncross-resistant alkylator-based, chemotherapy regimens can cure most of the patients. There is no role for maintenance therapy or bone marrow transplantation. Studies report an 80–90% survival rate among adults with Burkitt lymphoma who are given popular regimens such as R CODOX-M-IVAC (the combination of cyclophosphamide, vincristine, doxorubicin and methotrexate with etoposide, ifosfamide and cytarabine), hyper-CVAD-RMA (the combination of cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine) and other similar regimens [32–35]. However, toxicities both short-term and long-term failures to complete the therapy and treatment-related mortality are major hurdles for delivering these intense regimens. The addition of rituximab to treatment regimens appears to improve the outcome [36]. The survival rate among adults with Burkitt lymphoma who are given an intermediate intensity infusional chemotherapy regimen EPOCH-R is more than 90%, and this regimen appears to be more tolerable in adults [37]. The German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia (GMALL) used a modified regimen that was better tolerated in older patients with a 5-year progression-free survival reaching nearly 60–65% in patients with Burkitt lymphoma older than 55 years [36]. The regimen to be employed is a clinical decision based on the patients' age and general condition. The role of prephase, supportive care including prophylaxis and management of tumor lysis syndrome is the cornerstone for the successful management of Burkitt's lymphoma.

6.2.3 Mantle Cell Lymphoma

Mantle cell lymphoma was recognized as a distinct entity in the 1990s, and with chemoimmunotherapy, the survival of patients has considerably improved. A subset of patients with mantle-cell lymphoma who present with blood and bone marrow involvement, splenomegaly can have an indolent course akin to low grade lymphomas [38]. Most patients with mantle-cell lymphoma require therapy sooner or later after diagnosis. The outcomes of mantle cell lymphoma with R CHOP alone are modest. High-dose cytarabine-based regimens have shown remarkable activity in these patients [39]. Autologous hematopoietic stem-cell transplantation during the first remission is often incorporated as part of the initial treatment [40]. Maintenance rituximab is recommended post auto transplant and in patients with complete remission post induction. Bendamustine and rituximab have shown improvement in progression-free survival as compared to RCHOP in patients deemed unfit for intensive treatment and ineligible for autograft [41]. The advent of small molecule inhibitors like ibrutinib, acalabrutinib and venetoclax in the relapsed refractory setting has led to more patients receiving these treatments.

6.2.4 Marginal Zone Lymphomas

Marginal zone lymphomas are divided into MALT lymphomas, nodal marginal zone lymphomas and splenic marginal zone lymphomas. MALT lymphomas are the most common type and occur predominantly in the stomach. In patients with gastric MALT lymphoma with *Helicobacter pylori*, eradication of the infection will often lead to a clinical remission. However, the presence of the t(11;18) translocation predicts a higher chance of treatment failure and increased risk of relapse. For patients with localized gastric MALT lymphoma who do not achieve complete remission following antibiotic use, radiotherapy is usually curative. For advanced MALT lymphoma, chemotherapy plus rituximab is superior to the use of either treatment alone. Patients with nodal marginal zone lymphoma are usually given chemoimmunotherapy. Splenic marginal zone lymphoma typically presents with splenomegaly, and blood and bone marrow involvement. Patients with concomitant hepatitis C virus infection might respond to eradication of the virus. For other patients with symptomatic disease, single-agent rituximab can lead to clinical remission and is a good option. In patients with advanced stage disease, bulky abdominal nodes and constitutional symptoms bendamustine and rituximab are recommended [41].

6.2.5 Small Lymphocytic Lymphomas/Chronic Lymphoid Leukemia

Small lymphocytic lymphoma/chronic lymphoid leukemia constitute a disease spectrum. Patients with SLL present with hepatosplenomegaly and lymphadenopathy. SLL with peripheral blood monoclonal B lymphocytosis (>5000/μL) is termed as chronic lymphocytic leukemia. The treatment approaches are hence similar for both these conditions, which include wait-and-watch policy, chemoimmunotherapy, purine analog-based chemotherapy, targeted therapy including ibrutinib, venetoclax, etc. or a combination of these.

6.2.6 Follicular Lymphoma

The long-term survival in these patients closely approaches that of the normal population especially in the rituximab era. Many patients will die with but not from their follicular lymphoma or its complications; hence, long-term toxicities and quality of life improvement should be the primary objectives of treatment in follicular lymphoma.

Traditionally, grades 1 to 3A are considered histologically low-grade FL, while 3B is treated as an aggressive lymphoma. Early stage includes stage I and II follicular lymphoma, can be managed by RT alone with curative intent [42]. Radiation therapy (RT) to the limited disease in this population achieves good local control, and nearly half of these patients remain disease free [43]. Patients with non-contiguous, multifocal or bulky stage II disease should be managed as advanced stage disease. For low tumor burden advanced stage disease, active monitoring ("watch and wait") may be considered without adversely affecting long-term outcomes [44]. The GELF criteria can help identify those patients with FL in whom immediate therapy, rather than a watch-and-wait approach, is more appropriate. However, clinical judgment should be given more precedence over mere presence of one or two GELF criteria (Table 4).

Chemoimmunotherapy remains established first-line treatment for symptomatic advanced stage follicular lymphoma [41]. Rituximab maintenance following induction therapy remains an option for PFS advantage but there was no benefit in overall survival or quality of life [45].

Table 4 GELF criteria

Bulky disease: nodal/extranodal tumor mass >7 cm diameter or ≥3 nodal sites, each >3 cm diameter
Symptomatic splenomegaly
Organ compression; pleural effusion or peritoneal ascites
Elevated lactate dehydrogenase or elevated serum β2 microglobulin levels
B symptoms: unexplained fever >38 °C; drenching night sweats; or loss of >10% body weight within 6 months
Lymphocyte count $>5.0 \times 10^9$/L
Cytopenias (granulocytes $<1.0 \times 10^9$/L; platelets $<100 \times 10^9$/L)

6.2.7 Peripheral T-Cell Lymphomas

Mature T-cell lymphomas, such as peripheral T-cell lymphomas, are much less common than their B-cell counterparts but have as many subgroups, which makes clinical trials difficult; hence, treatment guidelines are seldom based on the results of randomized trials. Accurate diagnosis remains an issue. No standard therapy exists for patients with peripheral T-cell lymphoma not otherwise specified. These patients have traditionally received regimens such as CHOP and receive an autologous hematopoietic stem-cell transplant during initial remission. However, some studies have not shown a definite benefit from the incorporation of an anthracycline in the treatment regimen for patients with peripheral T-cell lymphoma.

Specific subtypes of peripheral T-cell lymphoma need attention. For patients with ALK-positive anaplastic large T-cell lymphoma have the best outcome with an anthracycline-containing regimen such as CHOP or CHOEP [46]. Patients with ALK-positive anaplastic T-cell lymphoma have a better outcome than those with ALK-negative anaplastic T-cell lymphoma, but this improved outcome is perhaps partly age-related, and older patients with either ALK-positive or ALK-negative anaplastic T-cell lymphoma seem to have nearly the same outcome [47]. Patients with localized extranodal NK–T-cell lymphoma presenting in the nose or nasal sinuses can be managed majority of times with chemoradiotherapy. These patients seem to be particularly sensitive to chemotherapy regimens that include methotrexate and L-asparaginase [48]. Peripheral T-cell lymphomas expressing CD30 respond to the antibody conjugate brentuximab vedotin. Brentuximab vedotin is now being incorporated into front-line regimens and usually substitutes for vincristine in the CHOP regimen. ALK-positive anaplastic T-cell lymphoma can also respond to the ALK inhibitor crizotinib. Other chemotherapeutic agents such as pralatrexate, romidepsin, belinostat and alisertib all have activity in peripheral T-cell lymphomas and can be used in patients with relapsed or refractory disease.

7 Management of Hodgkin Lymphoma

HL is classified into three subgroups which has prognostic as well as therapeutic significance in management.

I. Early stage (stage I and II)
    (a) Favorable
    (b) Unfavorable
II. Stage II B bulky (treated as advanced disease)
III. Advanced disease (stage III and stage IV)

7.1 Early Stage Favorable

Treatment strategies for early stage HL have evolved from radiation therapy alone to combine modality and now chemotherapy alone approach in PET era. Previously, extended field radiation was considered the standard therapy. NCIC group in their first randomized clinical trial had shown that subtotal radiation therapy (±ABVD) versus ABVD (4–6 cycles) has similar rates of freedom from disease progression (87% and 92%, respectively). Though radiation techniques used were primitive in this study, the outcome with chemotherapy alone arm was 90% at 12 years [49].

In early stage favorable disease, GHSG HD10 study group randomized between two/four cycles of ABVD chemotherapy and 20/30 Gy IFRT in 2 × 2 factorial design with four arms early favorable group. There was no difference between the four groups with respect to their progression-free survival and overall survival. Regards response to therapy, progression-free and overall survival. After this study results, ABVD for two cycles followed 20 Gy RT became standard of care in early favorable HL [50]. PET-adapted approach was used in HD16 trial to omit radiation in patients who were PET CR after two cycles; however, there was significant loss in tumor control in chemotherapy alone arm (5-year PFS, 93.1% [95% CI, 90.7–95.5%] vs. 80.9% [95% CI, 72.2–89.7%]; $P = 0.0011$) when Deauville score of 4 was used as a cutoff for positivity [51]. UK RADAR study is currently exploring the use of brentuximab with AVD in early favorable disease with an intention to omit radiation.

7.2 Early Unfavorable

Early stage unfavorable HL includes all patients with Ann-Arbor stage I or II disease and the presence of at least one risk factor (Table 5). Combined modality treatment (chemoradiation) remains the standard of care for early unfavorable HL. Number of ABVD cycles and dose of radiation is well established from GHSG HD11 trial. This trial again had four arms with 2 × 2 factorial design based on number of type of chemotherapy (ABVD/BEACOPP) and radiation dose (20 vs. 30 Gy). All four arms had similar freedom from disease progression. With prolonged follow-up in HD 11 study, there was no difference in progression-free survival between ABVD and BEACOPP when consolidated with 30 Gy radia-

Table 5 Risk stratification of early Hodgkin lymphoma

Risk factors	EORTC	GHSG	NCIC/ ECOG
Large mediastinal mass (>1/3)	Yes	Yes	No
Histology other than LP/NS	No	No	Yes
Age	≥50	No	≥40
Extranodal disease	No	Yes	No
ESR ≥50 mm/h without B symptoms or ≥30 mm/h with B symptoms	Yes	Yes	Yes
Number of nodal area involved	≥4 nodal areas	≥3 nodal areas	≥4 nodal areas

LP lymphocyte predominance, *NS* nodular sclerosis

tion therapy (HR, 1.1; 95% CI, 0.7–1.5; $P = 0.8$) [52]. However, in GHSG HD14 trial, an intensified chemotherapy schedule consisting of two cycles of escalated BEACOPP followed by two cycles of ABVD and 30 Gy IFRT (2 + 2) was more effective than four cycles of ABVD [53].

7.3 Early-Stage Risk/Response-Adapted Frontline Therapy

In the PET era, there were attempts to de-escalate therapy by omitting radiation using response adaption and replacing with more cycles of chemotherapy [54]. Two major trials were designed based on this principle-H10 trial (EORTC/LYSA/FIL) and the UK NCRI RAPID trial [55]. H10 trial compared in both early favorable and early unfavorable HL in a standard arm of ABVD + RT vs. the experimental arm which was driven by interim PET response (after two cycles of ABVD). Early PET-2 identified two risk population. First, one early PET-positive group where BEACOPP improved progression-free survival (HR 0.42 95% CI = 0.23–0.74); however, overall survival benefit was of borderline significance (HR 0.52 95% CI = 0.19–1.07). In PET-negative cohort H10 failed to demonstrate noninferiority of progression-free survival in no RT arm in both the subgroups. However, in early unfavorable HL, difference between noninferiority margin and upper boundary of CI was marginal. Hence, six cycles of ABVD remain an acceptable alternative in clinical situations where radiotherapy needs to be avoided.

In the UK NCRI RAPID trial, early-stage HL patients (defined as stage I–IIA and nonbulky disease) with a PET negativity after three ABVD cycles were randomized either to 30 Gy IFRT or to observation only [56]. Those with a positive PET (defined as DS-3, 4 and 5) were treated with one additional ABVD cycle followed by 30 Gy IFRT. Results suggested inferior PFS in chemotherapy alone arm as compared to CMT arm (3-year PFS 97.1% IFRT vs. 90.8% NFT), with a difference of 6.3%.

Though the difference didn't cross non inferiority boundary and the trial was reported as noninferiority of chemotherapy alone approach as opposed to CMT. In both trials PFS benefit was in the range of 6–12% in CMT arm as compared to chemotherapy-alone arm. The decision of response adapted therapy should be taken by multidisciplinary evaluation and counseling with each single patient affected with early-stage HL.

To summarize, two cycles of ABVD followed by IFRT is the standard of care in early favorable HL. Chemotherapy alone approach will lead 6–8% detriment in progression-free survival which needs to be discussed in a multidisciplinary team. Four cycles of ABVD followed by ISRT remain the standard of care for early unfavorable HL. Chemotherapy alone approach seems reasonable approach with marginal loss in tumor control and this decision should be taken in a multidisciplinary tumor board.

8 Advanced Hodgkin Lymphoma

Advanced Hodgkin lymphoma patients includes Ann Arbor stage III and IV along stage II B patients with bulky disease. Both ABVD and e-BEACOPP followed by RT to bulky sites and residual disease sites remains valid options in advanced Hodgkin lymphoma. There are several trials comparing ABVD and e-BEACOPP in advanced HL, all of them has consistently shown a PFS benefit of using e-BEACOPP regimen with overall survival remaining the same. A recent meta-analysis has shown OS benefit with e-BEACOPP (PFS: HR, 0.54; 95% CI, 0.45–0.64; OS: HR, 0.74; 95% CI, 0.57–0.97) [57]. This survival advantage with e-BEACOPP comes at the risk of secondary acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) as well as permanent sterility (90% in males and 50% in females). At relapse after ABVD, patients get second chance by salvage chemotherapy followed ASCT which nullifies the PFS advantage with e-BEACOPP. It can lead to overtreatment and unnecessary toxicity in significant proportion of patients who were anyways would have been cured with ABVD. Probably response-adapted therapy is the way forward in advanced HL, which selects out the poor performers with ABVD chemotherapy.

8.1 Response-Adapted Therapy in Advanced Hodgkin Lymphoma

Three trials addressed this question of response-adapted approach in advanced Hodgkin lymphoma. One after two cycles of ABVD, i.e., UK RATHL and other two after two cycles of e-BEACOPP, i.e., HD18 trial and AHL 2011 trial [58–60]. In the UK RATHL trial, de-escalation approach bleomycin could be omitted without compromising the efficacy if PET-2 is negative (DS-1, 2 and 3). In the PET-2 positive (DS 4 and 5), which was seen in 16% patients, escalation to e-BEACOPP has resulted in improved 3-year PFS and OS rates (67.5% and 87.8%, respectively), which is superior to historical controls.

In order to limit the toxicity of e-BEACOPP, HD 18 trial was designed where PET 2-negative (DS-1, 2) patients were de-escalated to two more cycles of e-BEACOPP. PET-2-positive group (DS-3, 4 and 5) were randomized to six cycles standard e-BEACOPP versus 6# Re-BEACOPP (total eight cycles in each arm). In PET-2-positive group, 5-year progression-free survival was 89.7% (95% CI 85.4–94.0). Addition of rituximab didn't make any difference. In PET-2-negative group, 5-year progression-free survival in deescalated arm (four cycles e-BEACOPP in total) was 92.2% (89.4–95.0) which was noninferior to the standard six cycles e-BEACOPP.

AHL 2011 is a noninferiority trial from France and Belgium where all patients received two cycles e-BEACOPP and underwent PET-CT. The PET-negative patients were switched over to four cycles of ABVD regimen, the PET-positive patients continued on BEACOPPesc for an additional four cycles. The trial proved noninferiority of this approach to standard four cycles e-BEACOPP from HD18 trial.

In conclusion, PET-directed therapy for de-escalation to AVD after negative PET-2 post two cycles of ABVD can be the standard of care. However, use of e-BEACOPP as escalation strategy may be justified by using HD18/AHL2011 approach when there is high IPS at baseline (IPS >3). RATHL approach can be employed in those who have low IPS at baseline to avoid overtreatment and limiting the toxicity.

8.2 Role of Radiotherapy in Hodgkin Lymphoma

The German Hodgkin Study Group (GHSG) HD10 study established two cycles ABVD, and a dose of 20 Gy IFRT is standard of care in early favorable HL. In unfavorable disease, 30 Gy was needed if the standard ABVD regimen was used as opposed to escalated BEACOPP regimen where 20 Gy was adequate. For advanced stage HL, RT didn't improve outcome if added in CR (by CECT) after full systemic chemotherapy. However, it did show benefit in those who remained in PR (partial response) after the end of systemic chemotherapy [61]. However, the role of RT in patients with bulky disease was not clear in the PET era. A prospective randomized study from Italy (GITIL/FIL HD0607 trial) has shown that consolidative RT can be safely omitted in patients who base line bulky node (defined by size ≥5 cm) and attained CMR by end of treatment PET [43]. The GHSG demonstrated in the HD15 trial that after intensive chemotherapy with escalated BEACOPP, consolidative RT should be given in patients with lesions more than 2.5 cm and are FDG avid [43].

8.3 Long-Term Complications

Hodgkin lymphoma survivors are at increased risk of developing long-term side effects, ranging from direct damage to organ function to second malignancies. Relapse of Hodgkin lymphoma remains the main cause of morbidity and mortality for initial 10 years after treatment. The cumulative incidence of mortality due to cardiovascular diseases and second malignancy exceeds to the disease-related mortality beyond 10 years of treatment. Hence, long-term follow-up plan of these patients should incorporate tools to assess risk factors for cardiovascular diseases.

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Adult Myeloproliferative Disorders/ Myelodysplastic Syndromes/Overlap Syndromes

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Abbreviations

aCML	Atypical chronic myeloid leukemia
AML	Acute myeloid leukemia
CML	Chronic myeloid leukemia
CMML	Chronic myelomonocytic leukemia
DIPSS	Dynamic IPSS
ESA	Erythropoiesis-stimulating agents
ET	Essential thrombocythemia
FN	Febrile neutropenia
HMA	Hypomethylating agents
IPSS	International Prognostic Scoring System
JMML	Juvenile myelomonocytic leukemia
MD-CMML	Myelodysplastic CMML
MDS	Myelodysplastic syndromes
MP-CMML	Myeloproliferative CMML
MPN	Myeloproliferative neoplasms
PMF	Primary myelofibrosis
PV	Polycythemia vera
WHO	World Health Organization

1 Introduction

Myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) are clonal hematopoietic disorders that have distinct clinical features, bone marrow morphology, flow cytometry and cytogenetic and molecular features. The MDS are a diverse group of bone marrow failure syndromes characterized by peripheral blood cytopenias and an increased risk of transformation to acute myeloid leukemia (AML) [1]. On the other hand, MPN are disorders characterized by clonal proliferation of myeloid precursors leading to marrow stromal changes and extramedullary hematopoiesis [2]. Some patients have a mix of features of MDS and MPN; these are overlap syndromes between MDS and MPN. In the current 2016 World Health Organization (WHO) classification, the entities in the overlap syndromes include chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), atypical chronic myeloid leukemia (aCML), and MDS/MPN unclassifiable. In addition to this, a provisional entity MDS/MPN with refractory anemia with thrombocytosis (MDS/MPN-RA-T) has also been included in this 2016 classification [3]. In this chapter, we discuss MDS, MPN and overlap syndromes. JMML is a pediatric disease and will not be discussed here.

2 Epidemiology

In 2000, the World Health Organization reclassified MDS from disorders with uncertain malignant potential to malignant, and following this, in 2001, MDS became reportable in the United States [4]. According to estimates from the SEER database, the age-adjusted incidence rate for MDS was 3.6 per 100,000 population in 2001. From that, it reached to a maximum of 5.1 in 2007 and remained at the same level till 2010. Subsequently, there was a slight decline to 4.7 in 2011

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[4, 5]. Several western studies have consistently reported the median age to be >60 years [4]. Although reliable estimates of incidence are unavailable from India, reports do suggest that the median age is probably lower [6]. A study from AIIMS reported the median age to be 48 years [6] and another study from another institute reported the same as 55 years [7]. Although the precise reasons for this are unclear, there is speculation that this is probably because of biological differences [6].

Similar to MDS, MPN is also a disease of the elderly, with the median age being >60 years in most European and American studies [8, 9]. According to available data, the incidence of primary myelofibrosis (PMF), polycythemia vera (PV) and essential thrombocythemia (ET) ranges from 0.1 to 1, 0.4 to 2.8 and 0.3 to 1.7 per 100,000 per year, respectively. Although reliable epidemiology data from India are lacking, one hospital-based study showed that 0.01% of patients attending out-patient department of a general hospital had MPN [10]. Additionally, there is some data to suggest that, just like MDS, MPN also occurs at an earlier age. One study suggests that the median age is 44 and 53 years for JAK2-negative and JAK2-positive MPN, respectively [11]. Similarly, another study showed the mean age to be 45 in all patients with MPN other than CML [12].

Among the overlap syndromes, CMML is the commonest one in adults. The others are essentially rare illnesses [3].

3 Clinical Presentation

Patients with MDS present with symptoms associated with cytopenias (anemia being the most common), although a fraction of them can be asymptomatic at diagnosis. Both in Western and Indian studies, fatigue is the most common presenting symptom and is present in approximately 90% of patients [13, 14]. Breathlessness on exertion is present in more than one-third of patients [14]. Fever and bleeding manifestations are present in about 20–25% patients at time of diagnosis [13, 14]. About one-third patients have weight loss at the time of diagnosis [13]. Hepatosplenomegaly or lymphadenopathy is unusual and is present in <5% of patients [14]. If significant organomegaly or lymphadenopathy is present, diagnosis other than MDS should be considered.

The presentation of patients with MPN depends on the particular disease entity. Common symptoms in patients with polycythemia vera include headache, facial flushing and pigmentation. Fatigue, weakness, anorexia, weight loss and abdominal discomfort are common in patients with myelofibrosis. Abdominal discomfort is common in essential thrombocythemia. In contrast to MDS, nearly 80% patients with MPN have splenomegaly and about 15% have hepatomegaly [12]. Arterial and venous thrombotic events are most common in ET followed by PV, and are relatively uncommon in IMF. In general, the incidence of thrombotic events ranges from 1.6% to 2.2% during the early course of MPN [15].

4 Evaluation, Work-Up and Risk Stratification

The evaluation of any patient with suspected MDS or MPN (or overlap syndromes) begins with a history and physical examination. Careful attention to patient's symptoms is crucial because, often therapy is guided by the symptoms. Also, it is crucial to record the comorbid illnesses, performance status and physical findings—these are important parameters in deciding treatment and serve as the baseline for response evaluation (e.g., spleen size, hepatomegaly).

The laboratory evaluation of these patients begins with examination of complete blood counts (including reticulocyte count) and a peripheral smear (and also serum chemistries, electrolytes, coagulation profile, blood grouping, viral markers, nutritional work up as may be appropriate and ACSO, LDH and EPO levels where indicated). These baseline parameters help in risk stratification and are also important in response evaluation. This should be accompanied by bone marrow examination. Bone marrow examination forms the cornerstone of establishing the diagnosis of these disorders. Marrow evaluation should include marrow aspirate for morphology, flow cytometry (in those with suspected MDS), cytogenetic evaluation (including conventional karyotyping), molecular analysis and a bone marrow biopsy [16–18].

A detailed discussion of the blood and marrow morphologic findings is beyond the scope of this chapter; however, in a nutshell, it consists of dysplastic changes in the erythroid, myeloid and megakaryocytic lineage. To be relevant, dysplastic changes should be present in at least 10% nucleated cells of a particular lineage. Assessment of marrow (and peripheral blood) blast percentage is crucial in classification of MDS; at least 200 cells on peripheral blood film and at least 500 cells on marrow smears should be counted. Marrow cellularity should be assessed and may have some role in treatment selection (e.g., immunosuppressive therapy for hypoplastic MDS). Flow cytometry characteristically shows multiple immunophenotypic abnormalities. The ELN guidelines recommend obtaining a flow cytometry in all cases of suspected MDS. Cytogenetic analysis should include conventional karyotyping on at least 20 metaphases. Interphase FISH for recurrent abnormalities is useful in cases with inadequate metaphases or in those with normal karyotype. The FISH panel used at our center includes evaluation for deletion 20q, trisomy 8, deletion 5/5q and deletion 7/7q. It is important to note that among all the prognostic factors, cytogenetic abnormalities carry the highest weightage. For the purpose of prognostic scoring, the IPSS-R score (see below) assigns each cytogenetic abnormality to a risk group ranging from very good, good, intermediate, poor to very poor. This grouping can be found in several publications (and can be easily referenced online also). Although not mandatory currently (and currently not part of the risk stratification schemes), molecular analysis is becoming more and more relevant. Somatic mutations may be helpful in proving clonality especially when cytogenetics is noncontributory; many somatic mutations carry some prognostic significance. Additional work up may be indicated in some patients (e.g., all young patients with MDS should undergo evaluation for underlying Fanconi's anemia and evaluation for PNH clone should be done in patients with hypocellular marrow). With this information, patients with MDS should be classified according the WHO classification into distinct disease categories. The WHO classification system puts MDS into distinct diagnostic categories; these different entities differ in their risk of progression to AML and in their prognosis. In addition to categorization, the information obtained from above work up is also adequate to risk stratify patients with MDS. There are several risk stratification systems of which the International Prognostic Scoring System (IPSS) and revised IPSS (IPSS-R) are the most important. The IPSS categorizes patients into four prognostic categories (low, intermediate 1, intermediate 2 and high risk) and IPSS-R into five categories (very low, low, intermediate, high and very high-risk groups). Both these scoring systems are based on marrow blast percentage, cytopenias and cytogenetic abnormalities. These risk groups differ in their risk of progression to AML and in their overall survival. In addition, risk stratification is extremely important in planning therapy (as discussed below). From a therapeutic perspective, low-risk IPSS and intermediate 1 IPSS are often clubbed together as low risk MDS; intermediate 2 and high-risk IPSS are clubbed together as higher risk MDS [16, 17, 19, 20]. More recently, a new risk stratification system, the Molecular International Prognostic Scoring System (IPSS - M), which incorporates mutational analysis data has been devised for MDS.

Similar to MDS, the classification of patients with MPN also depends on clinical parameters, marrow findings and molecular characteristics. The marrow is hypercellular in MPN (except in the burnt-out phase of PMF) and marrow biopsy is extremely crucial for assessment of marrow cellularity and reticulin or collagen fibrosis. Bone marrow examination is not mandatory for confirmation of diagnosis of polycythemia vera; however, it is recommended to be done in all suspected cases. For suspected PMF and ET, marrow examination is essential to establish the diagnosis. CML should be excluded by cytogenetic and molecular in all suspected cases of CMPD since it has an entirely different treatment and prognosis. Molecular analysis for MPN should include JAK2 V617F, JAK2 exon 12 mutation, CALR mutations and MPL mutations; many more have been recently described. A prognostic significance of some of these mutations is beginning to be unraveled. Just like MDS, several prognostic scoring systems also exist for PMF. One of the early scoring systems was the Lille score, which has largely been replaced by the IPSS. The IPSS for PMF takes into consideration age, constitutional symptoms, hemoglobin, WBC count and peripheral blood blasts, and divides patients with PMF into four different risk categories (low, intermediate 1, intermediate 2 and high-risk groups). More recently, dynamic IPSS (DIPSS) and DIPSS plus scoring systems have been used. While the IPSS score is useful at predicting survival and the risk of leukemic transformation at the time of diagnosis, the DIPSS score (based on the same factors as the IPSS score) can been used for estimating the prognosis from any time point in the course of illness. The DIPSS score is further refined by adding platelet count, red cell transfusion need and karyotypic abnormalities to form the DIPSS plus score. More recently, a prognostic score incorporating the molecular abnormalities has also been proposed (MIPSS 70 and MIPSS 70 plus). Similar to MDS, the prognostic scoring in PMF also helps to guide treatment (see below) [2, 18, 21–23].

In contrast to PMF, the risk stratification in PV and ET primarily depends on age and prior history of thrombosis (and also platelet count to some extent in ET). However, just like PMF, the risk category does help in deciding treatment [18].

The work up remains the same for overlap syndromes. Patients with CMML can be classified into myelodysplastic CMML (MD-CMML) or myeloproliferative CMML (MP-CMML). Patients with CMML with WBC count of >13,000/cumm are classified as MP-CMML. These have a better prognosis compared to MD-CMML. In addition, the blast percentage in the peripheral blood and bone marrow also affect the prognosis. The cut-offs used for segregating the prognostic groups are similar to those used for classification of MDS. In addition, at least 10 recurring mutations have now been identified in CMML with varying degrees of prognostic significance; of these ASXL1 mutations strongly confer an adverse prognosis. For the non-CMML overlap syndromes, although there are no well validated risk stratification systems for overlap syndromes, there is some data to show that older age at diagnosis, higher leukocyte count at diagnosis and SETBP1 mutation are adverse prognostic factors. Patients with these adverse prognostic features may be considered as high-risk patients [3, 24].

5 Principles and Guidelines for Management

The spectrum of therapies that can be offered in MDS, MPN and overlap syndromes ranges from watchful waiting to allogenic HSCT. The choice of therapy should be carefully made taking into consideration the symptoms, risk categorization, age, comorbid illnesses, and several other factors. Since allogenic HSCT is the only curative treatment, it should be offered to all young fit patients. However, HSCT may not be feasible in a sizeable proportion of patients, given that these disorders are typically seen in elderly patients (who may have many other coexisting comorbidities). In those patients in whom transplant is not feasible, the goals of management include minimizing the consider symptoms associated with the disease and maintaining the quality of life. It may be noted that although there are well defined response criteria published both for MDS and MPN, these are primarily intended to be used in clinical trials and not in routine clinical care [2, 25].

For MDS, cytopenias (predominantly anemia) need to be addressed. Supportive care is very important for all patients, in the form of transfusions, management of thrombocytopenia, prevention and management of infective episodes and iron chelation. Therapy with hypomethylating agents (HMA) or chemotherapy may be needed in some patients as discussed below. However, HMA and chemotherapy are not curative in MDS.

For MPN, important aspects of supportive care include treating symptomatic organomegaly, prevention and management of thrombosis and/or bleeding, and cytoreduction to prevent complications associated with hyperleukocytosis. JAK2 inhibitors (ruxolitinib and others) are useful in selected patients as discussed below. However, as is true for MDS, the only curative treatment for MPN is also allogenic stem cell transplant.

For overlap syndromes, the principles are essentially similar to those of MDS and MPN. Treatment should include management of anemia, treating symptomatic organomegaly, and control of counts. In addition, the drugs used for these syndromes are similar to those of MDS and MPN. However, there are also some novel agents in clinical trials [3].

6 Medical Management Options for MDS

Watchful waiting: Patients with lower risk MDS (see risk stratification above) often have indolent disease, low risk of progression to AML and long survival. Studies have shown that about half of these patients will die of causes unrelated to MDS [16]. Other studies have shown that life expectancy of elderly patients (>70 years) with refractory anemia or MDS with isolated del (5q) is similar to that of the general population [26]. Such studies provide evidence that, patients with lower risk MDS can be kept under a period of watchful waiting without active treatment. Current ELN recommendations suggest watchful waiting for patients with primary MDS low IPSS risk category and asymptomatic cytopenia.

For symptomatic patients with lower risk MDS, the primary goals of therapy are improvement of the symptoms associated with cytopenias and improvement of quality of life. Anemia is the most common cytopenia. For patients with lower-risk MDS and absence of del 5q, erythropoiesis-stimulating agents (ESA) are often the first-line therapy. These benefit about two-thirds of the patients. A detailed review of the ESA is beyond the scope of this chapter and excellent reviews can be found elsewhere. Patients with del 5q MDS often show resistance to ESA or short-lived responses, and in these patients, lenalidomide is chosen as the first-line therapy. Second-line agents for treatment of anemia include immunosuppressive therapy (antithymocyte globulin, cyclosporine, or both), lenalidomide (in those in whom it has not been previously used), erythroid maturation agents such as luspatercept or HMA. Immunosuppressive therapy often benefits those patients with lower risk MDS who have hypoplastic marrow and/or a small PNH clone, normal karyotype, no excess blasts and HLA-DR*15 genotype. Luspatercept mainly helps transfusion dependent patients with ringed sideroblasts who have failed ESA therapy. Packed cell transfusions are required in those who do not respond to any of these therapies. In patients requiring regular or frequent packed cell transfusions, iron chelation therapy should be considered as per standard guidelines [16].

Isolated neutropenia is rare in lower risk MDS, and it is even rare to need therapy. G-CSF or GM-CSF can be used for the treatment of febrile neutropenia (FN), along with broad spectrum antibiotics and other standard supportive therapy for FN. Isolated requirements of G-CSF or GM-CSF is very rare.

For patients with thrombocytopenia and lower risk MDS, danazol, and TPO receptor agonists (romiplostim and eltrombopag) are available agents. Either of these produces a clinical benefit in about 60–75% of the cases [16, 17, 27].

For patients with higher risk MDS (intermediate 2 and high-risk IPSS), hypomethylating agents (HMA) with or without venetoclax are an important treatment option and represent the most often used/preferred first-line therapy. HMAs (with or without venetoclax) can be used as sole therapy (along with supportive care) for patients considered unfit for transplant or those unwilling for transplant for various reasons, or they can be used as a bridge to transplant. Azacitidine is associated with improved overall survival compared to best supportive care (or low- or high-dose chemotherapy) and hence is preferred among the two agents. Decitabine has not been proven in randomized trials to improve survival but is often used interchangeably with azacitidine. Azacitidine and decitabine have not been compared head to head in randomized trials in this situation. Because responses to these agents are often delayed, these must be given for at least 4–6 cycles. For patients who benefit from HMAs, these are often continued till disease progression or toxicity [16]. Other options like low-dose chemotherapy or high-dose chemotherapy are not preferred as first-line options due to the lack of robust data supporting survival benefit and because of toxicities [16].

For patients who relapse after HMA or those who progress on HMA, the options are limited and their prognosis is dismal. Options like high-dose chemotherapy, low-dose chemotherapy or lenalidomide, use of the alternative HMA or combination of azacitidine with lenalidomide may be considered. In spite of any treatment offered, the prognosis of such patients remains poor [28]. Participation in clinical trials should be considered wherever possible.

The only curative treatment for MDS is allogenic stem cell transplant, and it is important that all young fit patients are offered this treatment. All potentially eligible patients should have their HLA typing done as soon as diagnosis is established. The long-term survival post allogenic stem cell transplant depends on multiple factors (including the IPSS risk group, type of transplant, degree of HLA match and others) and ranges from about 30% to 60% [17].

7 Medical Management Options for MPN

Medical management of patients with MPN depends on several factors—the particular MPN (PV vs. ET versus PMF), symptoms, age, risk of thrombosis, and other factors. Apart from conventional therapies, ruxolitinib represents a relatively recent major breakthrough in the treatment of these disorders. Several new agents are also in development, either alone or in combination with ruxolitinib. It is important to understand where to place ruxolitinib and the newer agents in the management of patients with MPN. A careful attention to patient's symptoms and priorities are very essential in clinical practice of these chronic disorders [18, 29].

For patients with PV, thrombosis represents a major risk and results in significant morbidities. The risk stratification of PV is based on risk of thrombosis and the aim of therapy is to reduce the risk of vascular complications. Life-style modifications to reduce the cardiovascular risk, and in particular smoking cessation should be considered for all patients [18]. For low-risk disease, phlebotomy (to maintain hematocrit target of 45%) and low-dose aspirin are recommended [18]. For selected patients with low risk—those with increasing counts, or those with worsening splenomegaly or those who are unable to tolerate phlebotomy, cytoreductive therapy may be needed. For high-risk disease, cytoreductive therapy in addition to aspirin and phlebotomy may be needed. Hydroxyurea is the preferred first-line cytoreductive agent in these patients [18, 30]. Second-line therapies in patients not tolerating or not responding to hydroxyurea include interferon and ruxolitinib [18, 29, 30]. Interferon is the agent of choice in pregnant females if required [18]. At present, the use of ruxolitinib should be restricted to patients with worsening splenomegaly or intractable pruritus or intolerance to hydroxyurea [30]. Ruxolitinib produces responses in 50–60% of such patients [31, 32].

For patients with ET, similar to those with PV, the risk stratification is based on the thrombotic risk, and again, as in PV, the aim of therapy is to reduce the risk of vascular complications. Observation alone is recommended for patients with very low risk disease. For those with low and intermediate risk disease, aspirin is recommended, particularly in the presence of vasomotor symptoms. Patients with high-risk disease need cytoreductive therapy in addition to aspirin. As with PV, hydroxyurea remains the drug of choice for these patients. Other agents which may be used in the second-line setting include anagrelide, interferon, busulfan or ruxolitinib. However, the use of these agents should be restricted to very selected patients [18, 29, 30].

In contrast to PV and ET, the risk stratification of PMF is different and is based on parameters like hemoglobin, absolute neutrophil and platelet count, marrow blast percentage, cytogenetics and molecular abnormalities [33]. Hydroxyurea is probably the most common agent used in the treatment of PMF and is useful in control of leukocytosis and thrombocytosis, and in reducing the spleen size. Additionally, it also probably improves constitutional symptoms, bone pains and pruritus. Interferon may be used and is probably more helpful earlier in the disease course. However, although interferon leads to control of counts, it probably does not reduce spleen size. Agents that may be helpful in the treatment of anemia include ESA, prednisolone, danazol and the IMiDs. Thalidomide, lenalidomide and more recently pomalidomide all have been used in PMF and have shown some benefit [34–36]. Among these three agents, low-dose thalidomide (in combination with prednisolone) is probably the most active. The activity of lenalidomide (in combination with prednisolone) and pomalidomide is very modest.

Ruxolitinib is a JAK1/JAK2 inhibitor and is the first approved targeted therapy in PMF. In addition to improving the symptoms and reducing the spleen size, ruxolitinib is also associated with improvement in survival. The reason behind the survival advantage is unclear. However, improvement in cachexia and decrease in systemic inflammation have been speculated as putative mechanisms. In addition, it is also speculated that long-term therapy might stop the progression of marrow fibrosis and it has been shown to decrease the mutant allele burden. It is likely that ruxolitinib when used in patients with low and intermediate-1 IPSS disease might lead to better long-term benefits. Several other agents (e.g., Panabinostat, interferon, danazol) are being tested in combination with ruxolitinib. Also, the role of ruxolitinib before stem cell transplant, and its impact on transplant outcomes are areas of study [28, 37, 38]. Several second generation JAK inhibitors are currently in development.

Allogenic HSCT is the only curative treatment for MPN and should be offered to all patients with intermediate-2 and high-risk PMF. It is also indicated in selected patients with intermediate-1 disease (e.g., those with transfusion-dependent anemia, adverse cytogenetics, ASXL1 mutation, triple-negative disease, etc.). Stem cell transplants in myelofibrosis carry a higher risk of transplant-related complications and death (compared to many other disorders), and a long-term survival is achieved in about 30–40% of patients [18, 29]. Allogenic stem cell transplant is not discussed further here and is discussed further in a separate chapter.

8 Medical Management Options for Overlap Syndromes

For overlap syndromes, similar to MDS and MPN, allogenic HSCT remains the only curative option. For CMML, the classification into MD-CMML and MP-CMML helps to guide treatment—the former are treated like MDS, the latter like MPN. For the non-CMML overlap syndromes, the treatment should include treatment of anemia, use of hydroxyurea (or interferon) when necessary, a trial of ruxolitinib when hydroxyurea fails and use of conventional chemotherapy in event of transformation to AML. In addition to these, there are some novel agents in clinical trials [3, 24].

9 Prognosis with Current Therapy

With the introduction of several new therapies and drugs, and with improvement in the outcomes and safety of stem cell transplantation, the outcomes of patients with MDS and MPN have significantly improved in the last two to three decades.

As is true for several other malignancies, the prognosis for patients with MDS and MPN depends on several disease related characteristics, and patient characteristics (e.g., performance status, comorbid illness, fitness for therapy, etc.).

With current therapies, the median survival of patients with MDS ranges from less than 1 year (for patients with very high revised IPSS risk group) to nearly a decade for patients with very low risk group [19]. Within each subgroup, additional factors like transfusion dependency, genetic mutations and other parameters also affect the outcomes. Similar to MDS, the survival of patients with PMF ranges from about 2 years (for patients with high IPSS risk group) to more than 10 years for those with low-risk disease [33]. As research reveals novel molecular prognostic markers in MDS and MPN, the prognostics schema is likely to be revised in the future. These may help to more accurately estimate the expected survival of individual patients with these disorders. The survival of patients with PV and ET treated with conventional therapy typically spans decades, and in many subsets (like low-risk ET) is similar to that of the general population [29].

As stated previously, the only curative treatment for both MDS and MPN is allogenic stem cell transplant. Long-term cure with allogenic stem cell transplant occurs in 30–60% of patients with MDS and about 30% to 40% patients with PMF.

10 Treatment of Relapsed Refractory Disease and Palliative Care Measures

Patients with relapsed MDS including those with progress to AML and patients with MF who do not respond to usual therapy or transform to AML represent a major therapeutic challenge. Unfortunately, there are no good salvage therapy options for these patients, and their prognosis remains dismal. Options for these patients are discussed under medical management (see above) under individual disease entity. Even with transplant, the prognosis of such patients is guarded; a long-term survival is achieved only in about 10–15% cases. Wherever feasible, enrollment in clinical trials should be considered. With several targeted drugs, molecular profiling of such patients is likely to help identify patients who may benefit from specific targeted therapy. Several such therapies are in the pipeline; several new trials are anticipated. Novel drugs are likely to change the dismal outcome of these patients; however, this may not happen in the near future.

11 How We Do It at TMC

At our center, we have a hematolymphoid disease management group which caters only to patients with hematolymphoid malignancies. This group consists of medical oncologists, radiation oncologists, pathologists, hematopathologists, radiologists and nuclear medicine experts, molecular pathologists, and other allied staff like social service staff, etc. This group has been functional since 2007.

All patients with suspected MDS and MPN are evaluated by the members of this group. The basic work up consists of blood and marrow examination as outlined before. Supportive care as required is provided to all patients during the diagnostic work up. Additional work up is requested if required based on the results of the initial work up. After diagnosis, risk stratification is done. We follow the revised IPSS system for MDS and IPSS system for myelofibrosis.

In general, the management follows the guidelines as mentioned above. All young fit patients are evaluated by our transplant team for the possibility of undergoing this curative treatment. For those who are unfit for transplant or are unwilling for the same (including those in whom it is not feasible due to logistic or financial reasons), we treat by medical management as discussed above. For higher risk MDS, we start patients on HMA (with venetoclax whenever feasible). Although we prefer azacitidine, the two are often used interchangeably (more often due to issues with the availability and cost). We evaluate response by a repeat marrow examination after 4–6 cycles of HMA, and in those who are responding, we continue the HMA therapy usually for 12 months or longer. Standard supportive care is provided all throughout.

For MPN too, we follow the usual guidelines. Hydroxyurea is the standard first-line cytoreductive agent; ruxolitinib is reserved for those not responding to HU or progressing on HU or intolerance to HU. Again, just like MDS, all young and fit patients are offered HSCT.

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Plasma Cell Dyscrasias

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1 Introduction

Plasma cell neoplasms are a clonal proliferation of plasma cells that are terminally differentiated B-cells characterized by immunoglobulin secretion. It includes a wide spectrum of plasma cell disorders, from asymptomatic monoclonal gammopathy of unknown significance (MGUS) and smoldering myeloma (SMM) to symptomatic multiple myeloma (MM), to plasma cell leukemia (PCL). A small proportion of plasma cell neoplasms (approximately 5–6%) will present as a solitary plasmacytoma (SP), either in bone or extramedullary tissues. Definitions and diagnostic criteria for each category of plasma cell neoplasms are given in Table 1.

The majority of plasma cell tumors are diagnosed as multiple myeloma (MM) and usually affect older adults. It is a multifocal neoplasm originating in the bone marrow and is characterized by clonal proliferation of malignant plasma cells in the bone marrow, secretion of monoclonal protein (also known as M-protein) in the blood or urine, and multiple organ dysfunction [1]. It evolves from a premalignant condition clinically recognized as MGUS [2–4].

The first documented case of MM was reported by Solly in 1844 in a 39-year-old woman, Sarah Newbury, and approximately a year later it was followed by a well-described case of Thomas Alexander McBean "a highly-respectable tradesman," 45 years of age [5]. In 1873, J. von Rustizky introduced the term "*multiple myeloma*" first time, and 16 years later Otto Kahler described the disease and hence, was also referred as "Kahler's disease" [5, 6]. Since then the diagnosis and treatment of multiple myeloma have changed dramatically. There has been a huge improvement in our understanding of the pathogenesis of myeloma leading to the discovery of highly specific biomarkers which are routinely practiced in the in the management of MM. Over the years, the staging system has been revised multiple times to combine measures of tumor burden, biology and underlying genetics of the disease. Recent advances in therapy like high dose chemotherapy with autologous stem cell transplant and availability of novel drugs like protease inhibitors and immunomodulators have resulted in a marked improvement in overall survival [7].

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Table 1 Diagnostic criteria of plasma cell disorders

Plasma cell disorder	Diagnostic criteria [11, 17]
Non-IgM MGUS	• Serum monoclonal protein (non-IgM type) <30 g/L • Clonal bone marrow plasma cells <10% • The absence of end-organ damage, i.e., CRAB features or amyloidosis
IgM MGUS	• Serum IgM monoclonal protein <30 g/L • Bone marrow lymphoplasmacytic infiltration <10% • No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to the underlying lymphoproliferative disorder
Light-chain MGUS	• Abnormal FLC ratio (<0.26 or >1.65) • Increased level of the appropriate involved light chain (increased κ FLC in patients with a ratio >1.65 and increased λ FLC in patients with ratio <0.26) • No immunoglobulin heavy chain expression on immunofixation • The absence of end-organ damage, i.e., CRAB features or amyloidosis • Clonal bone marrow plasma cells <10% • Urinary monoclonal protein <500 mg/24 h
SMM	Both criteria must be met: • Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg/24 h and/or clonal bone marrow plasma cells 10–60% • The absence of end-organ damage, i.e., CRAB features or amyloidosis
MM	Clonal bone marrow plasma cells ≥10% or Biopsy-proven bony or extramedullary plasmacytoma and Any one or more of the following myeloma defining events: *Myeloma defining events*: • Evidence of end-organ damage (**CRAB** features) that can be attributed to the underlying plasma cell proliferative disorder, specifically: – *Hypercalcaemia*: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL) – *Renal insufficiency*: creatinine clearance <40 mL/min or serum creatinine >177 μmol/L (>2 mg/dL) – *Anemia*: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L – *Bone lesions*: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT Any one or more of the following biomarkers of malignancy: – Clonal bone marrow plasma cell percentage ≥60% on BMA or BMBx – Involved: uninvolved serum free light chain ratio ≥100 (using Freelite assay, UK) – >1 focal lesions on MRI studies with a minimum of 5 mm
Plasma cell leukemia	Presence of 5% or more circulating plasma cells in peripheral blood smears in patients otherwise diagnosed with symptomatic multiple myeloma (IMWG 2021)
Solitary plasmacytoma	• Biopsy-proven solitary destructive lesion of bone or soft tissue mass of clonal plasma cells • The absence of clonal plasma cells in bone marrow biopsy and aspirate • Normal skeletal survey and MRI (or CT) of the spine and pelvis (except for the primary solitary lesion) • The absence of end-organ damage, i.e., CRAB features
Solitary plasmacytoma *with minimal marrow involvement*	• Biopsy-proven solitary lesion with evidence of clonal plasma cells • Clonal bone marrow plasma cells <10% • Normal skeletal survey and MRI (or CT) of the spine and pelvis (except for the primary solitary lesion) • The absence of end-organ damage, i.e., CRAB features
POEMS syndrome	Mandatory criteria • **P**olyneuropathy • **M**onoclonal plasma cell proliferative disorder (almost always λ) Any one of the following three other major criteria: • Sclerotic bone lesions • Castleman's disease • **E**levated levels of VEGF Any one of the following six minor criteria: • **O**rganomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) • Extravascular volume overload (edema, pleural effusion, or ascites) • Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) • **S**kin changes (hyperpigmentation, hypertrichosis, glomeruloid haemangiomata, plethora, acrocyanosis, flushing, white nails) • Papilloedema • Thrombocytosis/polycythaemia
Systemic AL amyloidosis	• Presence of an amyloid-related systemic syndrome (e.g., renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement) • Positive amyloid staining by Congo red in any tissue (e.g., fat aspirate, bone marrow, or organ biopsy) • Evidence that amyloid is light-chain-related established by direct examination of the amyloid using mass spectrometry-based proteomic analysis, or immunoelectron microscopy • Evidence of a monoclonal plasma cell proliferative disorder (serum or urine monoclonal protein, abnormal free light-chain ratio, or clonal plasma cells in the bone marrow)

2 Incidence and Epidemiology in India and Global

2.1 Monoclonal Gammopathy of Unknown Significance and Smoldering Myeloma

MGUS affects approximately 3% of Caucasians over the age of 50 years with 1% average annual risk for progression to MM. The usual sequence of development of monoclonal gammopathies is MGUS progress to smoldering multiple myeloma (SMM) and then MM, which may progress finally to PCL [7]. Approximately 25% of patients with MGUS develop MM after a follow-up of more than 20 years. However, SMM carries a higher risk of progression to frank multiple myeloma (10% per year the first 5 years) compared with MGUS [2–4, 8–10].

2.2 Multiple Myeloma

MM is the second most common adult hematologic malignancy accounting for approximately 1–1.7% all of the cancers and 10–13% of hematologic neoplasms (Fig. 1) [1, 11]. The incidence of MM varies in different parts of the world, and it has been reported higher in western countries like the United States, European countries, Australia, etc. but is lesser in Asian countries [7, 12]. The estimated world-wide 5-year prevalence is approximately 230,000 patients [13]. The median age of patients at diagnosis is approximately 66–70 years with 37% of patients younger than 65 years of age and is extremely rare in those less than 30 years of age with a reported frequency of 0.02–0.3% [12]. Although robust data on the incidence of MM in India is lacking, considering the probability of 0.1% of the development of MM in elderly, it affects a large group of population [14]. The annual incidence of MM in the Indian population is considered in between 0.35 and 0.96 per 1,00,000 population [7]. The median age of MM patients is approximately a decade younger than western population, i.e., 56 years (range, 29–85 years) [15, 16].

2.3 Solitary Plasmacytoma

SP is an uncommon lesion and accounts for only 1–2% of plasma cell neoplasms (Figs. 2 and 3). Males are affected more than females and the median patient age at diagnosis is approximately 55 years [17]. Although the incidence of SP in India is not known, the median age is 53 years and M:F ratio of 2.2 [18].

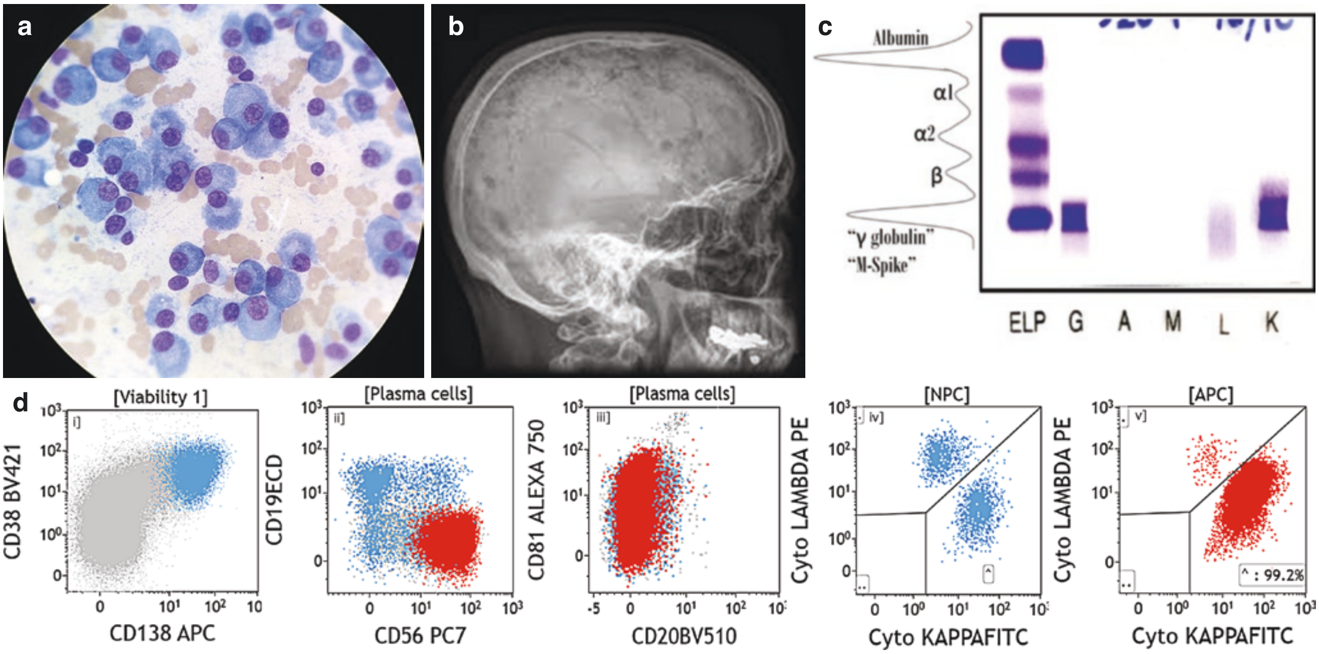

Fig. 1 (**a**) Microscopic picture (oil immersion, 100×) of bone marrow aspirate smear with markedly increased plasma cells in a case of multiple myeloma. (**b**) X-ray of skull with multiple lytic lesions. (**c**) Results of serum protein electrophoresis and immunofixation demonstrating "M-spike" with IgG-Kappa type M-protein. (**d**) Dot plots "(i) to (v)" of flow cytometric immunophenotyping. Dot plot "(i)" shows CD38 and CD138 positive plasma cells (light blue dots). Dot plots "(ii) to (v)" show abnormal clonal plasma cells (red dots) demonstrating abnormal negative expression of CD19, over-expression of CD56 and kappa-light chain restriction

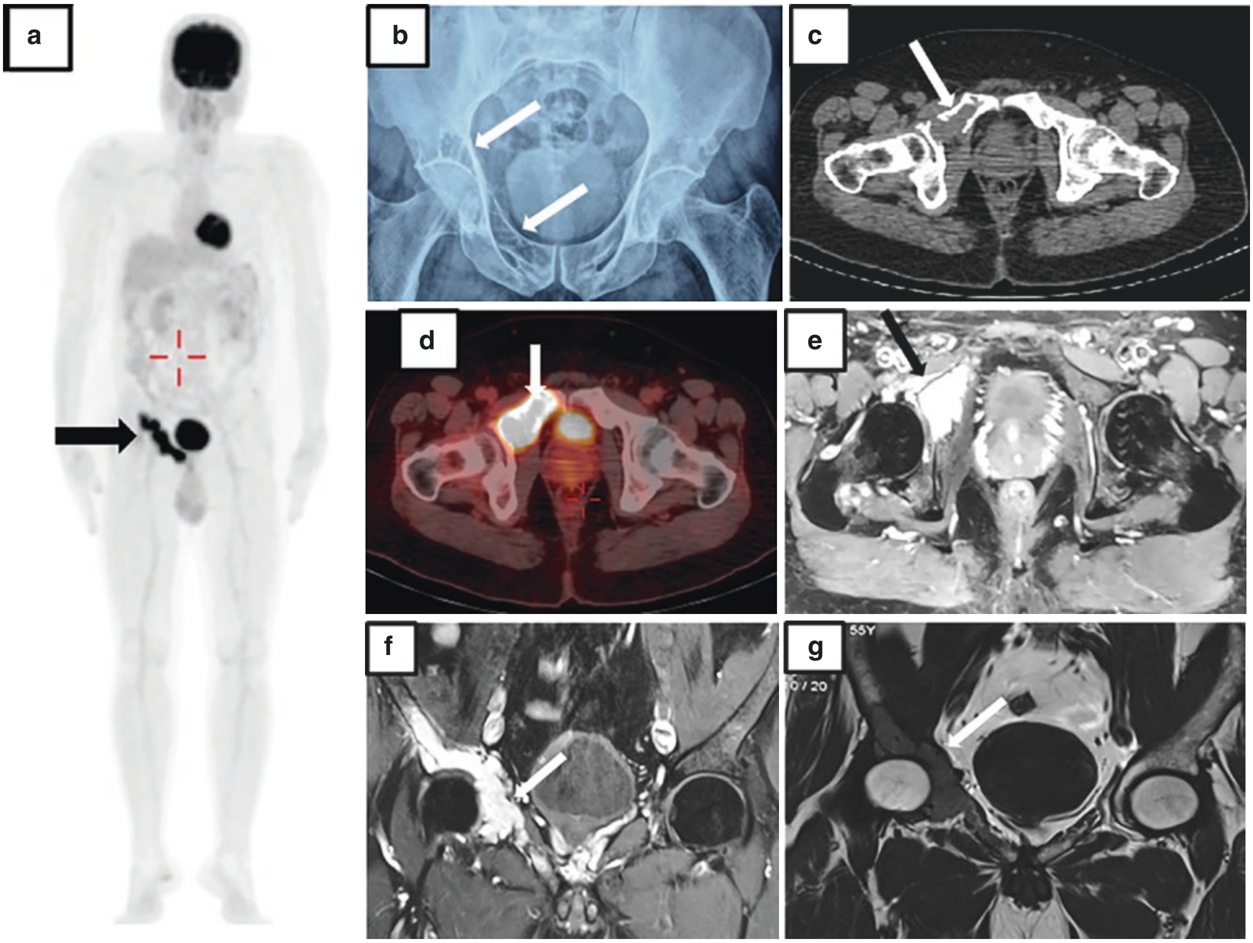

Fig. 2 (**a**) Maximum intensity projection of whole-body PET–CT scan showing an avid pelvic bone solitary plasmacytoma. (**b**) X-ray pelvis showing an osteolytic lesion involving the right iliac and pubic bone. (**c**) Axial section of the computerized axial tomography scan showing the lytic bone destruction of the right pubic bone. (**d**) Corresponding PET image showing increased uptake in the lytic bone lesion. (**e**) Axial T1 contrast magnetic resonance imaging (MRI) showing the contrast-enhanced lesion in the right pubic bone. (**f**) Coronal plane image showing the extent of the lytic bone destruction. (**g**) Coronal T2-weighted MRI showing hypointense signal in the region of the bone lesion

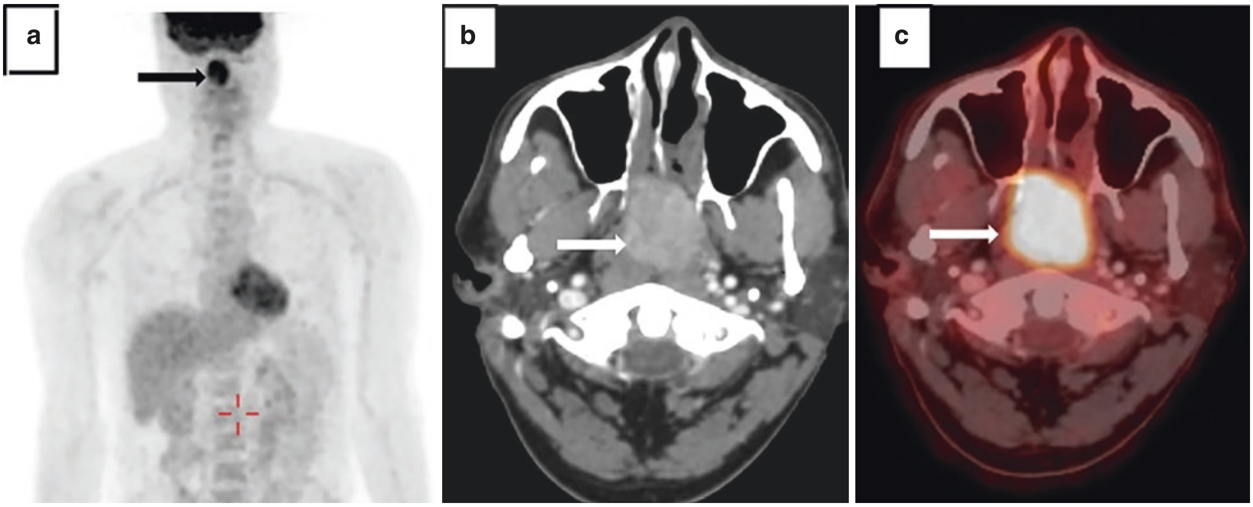

Fig. 3 (**a**) Maximum intensity projection of PET–CT with an avid nasopharyngeal extramedullary plasmacytoma. (**b**) Corresponding axial CT image showing the nasopharyngeal extramedullary plasmacytoma. (**c**) Corresponding axial PET image showing increased uptake in the nasopharyngeal extramedullary plasmacytoma

2.4 Systemic (AL) Amyloidosis

It is a relatively uncommon disease with an incidence of 3–5 cases per million population in the USA, approximately one per 100,000 population in UK, and 3.2 per million person-years in Sweden [19].

3 Etiology and Pathogenesis

The cause of plasma cell neoplasm (PCN) is still unknown. Several studies have evaluated potential risk factors responsible for development that included exposure to radiations, pesticides, hair dyes, benzene and petroleum products, etc. However, a little evidence is available to support a causal relationship with the development of PCN [7, 20, 21]. PCN are as such not genetic diseases; however, a few familial cases highlighting genetic inheritance for this disease have been reported [22–25].

MM is a characterized by uncontrolled proliferation of malignant plasma cells that are derived from post-germinal-center B cells. Multistep genetic and microenvironmental changes lead to the transformation of these cells into a malignant neoplasm. In germinal centers of lymphoid organs, B cells undergo affinity maturation, somatic hypermutation, and isotype class-switch recombination that result in the production of antibodies with a high affinity for specific antigens [1, 26]. In a predisposed person, the process of somatic hypermutation and class-switch recombination leads to aberrant fusions of DNA and chromosomal translocations. Rarely, these translocations involve specific oncogenes that give cells a growth advantage leading to the development of clonal plasma cells which initially constitutes a premalignant condition, i.e., MGUS which progress to SMM and eventually multiple myeloma. Common translocations involve IGH region of genes on chromosome "Ch 14" and a set of recurrent partner genes, such as NSD2 (also known as MMSET) & FGFR3 [t(4;14)], MAF [t(14;16)], MAFB [t(14;20)], and Cyclin-D1 [t(11;14)] & Cyclin-D3 [t(6;14)] [7, 27]. Recently, MYC was identified as a deregulated factor in up to 50% of patients. Thus, chromosomal translocations are a possible initiating event for a subset of MM cases. Another possible genetic alteration that may be involved in the initiating events responsible for almost half of this disease is a hyperdiploidy (chromosomes >46), a frequent form of aneuploidy. The secondary genetic events associated with MM include genetic mutations like RAS genes (K-ras/N-ras), FAM46C, DIS3 TP53, and others [28–31]. These mutations can affect several cellular signaling pathways (NF-κB pathways and MAPK pathway) and alter the cell apoptotic and proliferation mechanism and may be involved in the disease progression of MGUS to MM [29, 32, 33].

Besides genetic factors, bone marrow microenvironment, and immune reconstitution also play a vital role in the pathogenesis of MM. The interaction between the proteins like vascular cell adhesion protein 1 (VCAM1), CXC-chemokine ligand 12 (CXCL12) expressed the on the cell surface of bone marrow stromal cells (BMSCs), osteoblasts, endothelial cells and proteins expressed on the myeloma cells like CXC-chemokine receptor type 4 (CXCR4), integrin results in the secretion of several cytokines and chemokines which creates a favorable environment for cell proliferation, migration, and inhibition of apoptosis for MM cells [34–39]. Additionally, macrophages also produce factors like IL-1β that interacts with BMSCs and induce IL-6 secretion [39, 40]. Likewise other cell types, including T cells, B cells, monocytes, and multiple myeloma cells, also produce IL-6, which promotes proliferation of multiple myeloma cells and resistance to apoptosis contributing to the progression of this disease [40]. Immune-cells like T-cells, NK cells, dendritic cells and myeloid-derived suppressor cells (MDSCs) also constitute an integral component of microenvironment and show quantitative as well as functional impairment with the advancement of disease through "antigen-specific T-cell tolerance" [41, 42]. Thus, pathogenesis and disease progression in MM is a multifactorial biological process that involves genetic, microenvironmental, and immunological factors.

Other plasma dyscrasias caused due to the proliferation of monoclonal plasma cells and secretion M-protein include systemic amyloidosis and POEM syndrome. Pathogenesis of POEM syndrome is not understood yet but is multiorgan affecting disease as a result of the paraneoplastic process associated with the monoclonal lambda plasma cell disorder and possibly caused by increased levels of proinflammatory cytokine milieu [43]. Systemic amyloidosis also referred as "AL amyloidosis" and is a result of the extracellular deposition of monoclonal immunoglobulin light chains that forms the amyloid [44].

4 Clinical Presentation

Clinical manifestations of the MM are primarily caused by neoplastic plasma cells and monoclonal protein and/or cytokines secreted by them. The common clinical manifestations of the MM include signs of end-organ damage, such as hypercalcemia (C), renal insufficiency (R), anemia (A), and/or bone disease (B) with lytic or pathological fractures [9]. These manifestations are collectively known as CRAB features. Although most of the MM patients are characterized by the secretion of a M protein, approximately 15–20% of patients are associated with only monoclonal free light chains secretion (also referred as "light chain myeloma"), and, in <3% of patients these cells secrete no monoclonal protein (also referred as "non-secretory myeloma") [10, 11].

The usual symptoms of MM include bone pain (e.g., back pain), weakness, fatigue, weight loss, recurrent infections, easy bruisability, and increased bleeding tendencies etc. These symptoms reflect manifestations of underlying lytic bone lesions, anemia, hypercalcemia, thrombocytopenia, and hypogammaglobulinemia. A study of 1027 MM patients from Mayo Clinic, Rochester, MN (USA) reported the frequency of clinical symptoms at presentation that included bone pain in 58%, fatigue (usually related to anemia) in 32%, weight loss in 24%, and other symptoms like paresthesia (5%), fever (0.7%), etc. [6]. A recent data of 3988 MM patients from the Swedish Myeloma Registry documented osteolytic lesions or compression fractures in 77%, anemia in 49%, impaired kidney function in 18%, and hypercalcemia in 13% patients [45].

Patients with POEMS syndrome usually present with clinical features related to polyneuropathy that includes weakness, numbness, and tingling in the legs and arms, organomegaly like hepato-splenomegaly and few times symptoms like fatigue, swelling in your limbs, sexual problems, those are caused by underlying endocrinopathy like diabetes, hypothyroidism, and problems with metabolism, etc. [43, 46]. The clinical presentations of AL amyloidosis diverse and depends on the organ of involvement [19, 47]. It usually affects the heart, kidneys, liver, spleen, nervous system and digestive tract. Severe forms of amyloidosis can lead to organ failure and ultimately death. The pathognomonic clinical presentation of AL amyloidosis includes a macroglossia and periorbital purpura, but these does not occur in more than one-third of all cases [19, 47].

5 Evaluation and Work-Up Including Risk Stratification

Recently updated diagnostic criteria for the diagnosis of PCN are given in Table 1 [11]. Hence, for the diagnosis and classification of the PCN, each patient must be evaluated for the laboratory and radiological factors.

5.1 Initial Work-Up

The initial work-up for patients suspected of having a plasma cell dyscrasia should include:

- Complete blood count with differential count and platelet count
- Serum protein electrophoresis and immunofixation to quantitate and define protein type
- A routine serum chemistry panel (to include calcium, blood urea nitrogen, creatinine)
- Bone marrow aspirate with flow cytometric immunophenotyping and BM biopsy to assess clonal plasmacytosis
- Serum beta-2-microglobulin
- Serum albumin and globulin levels
- Serum free light chain assay
- 24-Hour urine protein, electrophoresis, and immunofixation
- Quantitative serum immunoglobulin levels
- Low dose whole body computerized tomography scan, PET-CT, MRI or Skeletal survey (bone scans contribute little since isotope uptake is often low in purely lytic bone disease)
- Cytogenetics, including FISH (fluorescence in situ hybridization) on bone marrow plasma cells

5.2 Additional Work-Up

Useful data may be obtained by analysis of

- Plasma cell labeling index (PCLI)
- Ploidy analysis
- Immunophenotyping using flow cytometry in bone marrow
- Circulating plasma cells (CPC) using flow cytometry or immunofluorescence
- Lactate dehydrogenase (LDH) levels
- Minimal residual disease (MRD) monitoring

The therapeutic response and clinical outcome in MM patients are significantly heterogenous to the given treatment. This heterogenicity in the overall clinical outcome is alike any malignancy dependent on many factors that include host factors, tumor burden (stage), tumor genetics (cytogenetic abnormalities). Traditionally, tumor burden in MM has been assessed using the International Staging System (ISS) [48] and the Durie Salmon Staging (DSS) [49]. Recently, International Myeloma Working Group (IMWG) has revised the ISS and incorporated the cytogenetic abnormalities (R-ISS) (refer to Table 2) [50]. After the diagnosis of MM

Table 2 Revised International Staging System for MM [50]

Stage	Criteria
Stage-I	ISS-I (serum albumin >3.5, and serum beta-2-microglobulin <3.5) No high-risk cytogenetics Normal LDH
Stage-II	Neither stage I or III
Stage-III	ISS stage III (serum beta-2-microglobulin >5.5) High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or Elevated LDH

LDH lactate dehydrogenase, *ISS* International Staging System

Table 3 Risk factors associated with multiple myeloma

Risk factors		Prognosis	References
Cytogenetics	Trisomies, t(11;14), t(6;14)	Good	[51, 52]
	t(4;14), gain(1q)	Intermediate	
	t(14:16), t(14;20), del(17p)	Poor	
Flow cytometry	MRD negative status	Good	[7, 53–59]
	Higher number of circulating plasma cell numbers	Poor	[60–62]
	>5% normal PC cells in BM	Good	[63]
	MGUS-like immunophenotypic signature	Good	[64]
	CD81 expression (>25%)	Poor	[65–68]
	CD117 expression (>50%)	Good	[67, 68]
	High plasma cell proliferative rate (PCLI)	Poor	[68]
Molecular	High-risk gene expression signatures (GEP70 and HOVON, among others)	Poor	[7, 16, 51, 69–72]
	TP53 mutations	Poor	
Other factors	Extramedullary disease	Poor	
	Renal failure	Poor	
	Poor performance status	Poor	
	Immunoparesis	Poor	
	Plasmablastic morphology	Poor	

patients are evaluated for the risk stratification and to determine additional prognostic factors that include biochemical, morphological, immunophenotypic, cytogenetic and molecular factors. The list of additional prognostic factors and their value in the management of MM is stated in Table 3. The common radiological features include lytic lesions, pathologic fractures, compression fracture, and osteoporosis.

6 Minimal Residual Disease (MRD) Monitoring

Several recent studies have established the major role of MRD status in the response assessment and prognostication in MM treated with autologous stem cell transplant (ASCT) [54, 55, 57–59, 73–82]. MRD negative status has been highly correlated with progression-free survival (PFS) and overall survival (OS). In MM, for a long period, MRD evaluation was not perceived because of the inability to achieve complete response (CR) with available treatments. However, newer treatment modalities now allow achieving the CR in a large majority of patients, including a significant proportion with stringent immunophenotypic CR [83–87]. Hence, international myeloma working group (IMWG) has included flow cytometric absence of clonal plasma cells in bone marrow as a criterion to define stringent CR (sCR) [57, 59, 74].

MRD can be monitored by either MFC or by molecular techniques. Molecular techniques such as allele-specific oligonucleotide (ASO) PCR, when compared with 3–4 color MFC, have greater sensitivity 23; but time-consuming, labor-intensive, and applicable in a limited number of patients [54, 55, 57, 73, 75, 88–90]. Recent reports on the application of high-throughput sequencing (next-generation sequencing, NGS) appears to be relatively easier but the experience and knowledge of this methodology still premature and limited by laborious standardization and bio-informatics [53]. On the other hand, 8–10 color flow cytometry can be equally or more sensitive technique. MFC applies to a greater proportion of the MM patient population, less time-consuming, and provides sensitivity below the cutoff levels considered to be clinically useful [57, 74]. New methods of flow cytometric MRD monitoring using novel approaches is referred as next-generation flow cytometry (NGF) that is shown to be a highly effective way of MRD monitoring in MM [57]. Thus, MRD status and depth of log reduction in MRD levels by MFC have independent clinical relevance in the monitoring of MM patients and to develop the individualized approach in the management of the disease [79].

7 Principles of Management

Plasma cell dyscrasia represents a spectrum of clonal plasma cell disorder ranging from MGUS to multiple myeloma/plasma cell leukemia, each with differing biology, prognosis requiring specific treatment approach. As the impact of early therapy is being explored in clinical trial setting, in clinical practice patients with multiple myeloma defined as per IMWG guidelines are considered for therapy. Plasmacytomas are treated with local therapy and can be cured in majority of patients, while disseminated disease in multiple myeloma patients requires them to be treated with systemic therapy. Multiagent induction therapy using novel agents followed by consolidation and maintenance is recommended in most of the patients as deeper and long lasting remission achieved with such an approach are associated with improved long term outcomes. Besides anti plasma cell therapy, supportive care like bone strengthening agents, renal support, prevention, and prompt treatment of infections is important for optimal outcomes. Despite all these advances, multiple myeloma remains incurable and continuous follow for timely retreatment is important.

8 Medical Management and Monitoring

8.1 Indications for Systemic Therapy

Patients who meet criteria for multiple myeloma as described above are considered for systemic therapy. Although early therapy for patients who do not meet these criteria has been shown to benefit in patients with high-risk smoldering myeloma, this needs further confirmation [91].

8.2 Therapy for Newly Diagnosed Myeloma

The approach depends on patients risk stratification and eligibility for ASCT. Decision on transplant eligibility can be guided by available published literature to determine the risk-benefit assessment and physiological age is considered than the exact chronological age cutoffs. Most of patents selected at our center for ASCT are less than 65 years of age with ECOG performance status of 0–2. ASCT is usually not recommended in presence of severe compromised heart function (NYHA class 3 or 4) and liver cirrhosis. Traditionally, renal dysfunction is not considered a contraindication for transplant but despite reduced dose melphalan conditioning, limited literature available suggests higher associated toxicities and this needs to be factored in the decision making.

8.3 Initial Therapy

ASCT eligible patients are treated with 3–4 cycles of induction regimen followed by stem cell harvest. There is some emerging evidence that ASCT can be deferred until first relapse [92]. Such an approach requires stem cells be harvested and stored for future use in first few months from diagnosis as risk of failure of mobilization at a later time point may preclude this important consolidation strategy. Besides individual patients risk stratification and comorbidities suggesting a particular regimen to be preferentially suitable for individual patient, availability of salvage options, and ASCT needs to be considered in Indian context. Patients ineligible for ASCT or where upfront ASCT is deferred needs consolidation (usually with same as induction regimen) for a total of 8–12 cycles before initiating maintenance therapy.

VRd regimen has been shown to have survival advantage over Rd and represents one of the current preferred regimens for upfront therapy [93]. Alternative Bortezomib-based induction regimens include VTd and VCd. These regimens were used commonly outside USA due to regulatory issues with lenalidomide in European Union and lack of availability of potent salvage regimens in LMICs or in individual patients with renal dysfunction [94]. KRd (Carfilzomib–Lenalidomide-low-dose dexamethasone) has been shown to be active in many single-arm studies and was recommended for high-risk patients, however based on recent data it is not recommended for NDMM [95]. Daratumumab-based induction therapy is associated with better PFS; however, the comparative phase III study comparing it with VRd is awaited. For patients with advanced age, poor performance status or comorbidities, lenalidomide-low dose dexamethasone (Rd) is an active regimen with good tolerance and better outcome and addition of Daratumumab can be considered based on result of MAIA study. Multi-agent-based regimens using anthracyclines and platinum (VTD-PACE, DCEP, etc.) are particularly useful in aggressive disease such as plasma cell leukemia or patients with multiple extra-medullary plasmacytomas [96]. Unless there is need of initial rapid disease control, as a part of combination induction regimen, once a week subcutaneous bortezomib and low-dose dexamethasone (40 mg weekly) is preferred over intravenous/twice weekly bortezomib and high-dose dexamethasone, respectively [97, 98]. In patients with renal dysfunction, Lenalidomide needs be dose modified or avoided. Plasma exchange with aggressive systemic therapy with VTd or VCd may be considered for patients with cast nephropathy and acute renal failure.

8.4 Autologous Stem Cell Transplant (ASCT)

ASCT is associated with deep and long-lasting remission and remains standard of care despite improved outcomes with novel agent-based therapies. It is safe and equally effective in Indian setting and represents important treatment option given the lack of availability of salvage options. Timing of ASCT has been the question of some of the recent large randomized controlled studies, and there is suggestion that ASCT can be delayed till first relapse but cannot be omitted from therapy of myeloma. Given the logistic difficulty with storing stem cells and limited therapeutic options in relapsed setting, ASCT is best done in upfront setting in our patients. Clinical utility of tandem ASCT is diminishing with advent of novel agents, however, probably young high-risk patients may possibly benefit by this approach [100].

8.5 Post ASCT Consolidation/Maintenance

The role of post ASCT consolidation has been recently challenged in the recent era. BMT-CTN 0702 studied the isolated effect of consolidation RVd for 2 cycles and seems to have no added benefit and hence patients should proceed to maintenance after ASCT [99].

8.6 Maintenance Therapy

Maintenance therapy is recommended for patients following ASCT as well as in ineligible patients after 8–12 cycles of initial therapy as it is shown to be associated with survival advantage [101, 102]. Lenalidomide is recommended for most of the myeloma patients except high risk patients who may benefit by addition of bortezomib to lenalidomide for maintenance therapy. Continuous therapy with longer maintenance seems best in term of PFS; however, optimal duration of maintenance therapy is still not known and one must take into account patient's tolerance, long-term side effects for, e.g., secondary malignancy with lenalidomide, depth of remission as assessed by MRD, patient's preference, etc. and an individualized decision whether to stop maintenance need to be made from case to case basis particularly in non-high-risk patients.

8.7 Prognosis with Current Rx

Revised ISS staging system is commonly used to stage and prognosticate myeloma patients. It is good and powerful system to predict outcomes. Five-year predicted overall survival as per this system for R-ISS I, II, and III is 82%, 62%, and 40%, respectively, while PFS for these three groups are 55%, 36%, and 24%, respectively [50]. Outcomes are rapidly improving and physician and patients alike should be aware about time gap required for survival improvements to reflect the current literature.

8.8 Management of Recurrent Disease Including Specific Palliative Measures

Almost every patient with multiple myeloma relapses, with shortening of remission with each subsequent line of therapy [103]. The prognosis of refractory myeloma is grave with PFS and OS less than 6 and 12 months, respectively, with conventional salvage regimens with novel agents and chemotherapy [104]. While choosing salvage regimen many factors needs to be considered for optimal outcomes. These include remission depth and duration, tolerance to first-line therapy, aggressiveness of relapse, current medical condition of patient, and general condition as assessed by ECOG performance status of patient. Also one needs to make a decision whether a given patient is transplant candidate at time of relapse. Usually fit patients who have not had ASCT earlier or had one as a part of frontline therapy with excellent response (e.g., remission typically lasting more than 36 months with maintenance and more than 18–24 months without maintenance. Usually a triplet with two new drugs to which patient is not refractory is used in salvage regimen preferably with CD38 monoclonal antibody. An early use of daratumumab is recommended given the shorter PFS and poor tolerance in later lines. Patient, who relapses after 6–12 months from stopping of initial regimen, may be considered sensitive and retreated with same drugs. Some patients with indolent relapse or frail patients may be treated with doublets. Patients with aggressive relapse may be treated with multiagent chemotherapy regimen-like VTD-PACE, etc. Duration of second-line regimen has not been studied very well and patients achieving a plateau in response may be considered for stopping of therapy on case to case basis. In refractory patients, one may consider drugs like melphalan/doxorubicin/ bendamustine-based regimen, panobinostat with bortezomib, quadruplet regimens of monoclonal antibody on case to case basis. CAR-T and BiTes have been recently approved and represent relapsed myeloma patients and potentially represent a meaningful treatment options whenever feasible.

9 Role of Definitive Radiation Therapy (RT) for Solitary Plasmacytoma

Solitary bone plasmacytomas (SBP) are radiosensitive tumors with excellent long-term local control with RT (79–91%) [105–111]. For SBP the local tumor and potential local microscopic disease require RT treatment. For solitary extramedullary plasmacytomas (SEP), RT is considered curative strategy. Approximately 25% of SEP in the head and neck region will have regional nodal disease on imaging (MRI and PET/CT) [111]. Therefore, prophylactic radiotherapy to uninvolved nodes is controversial, especially SEP's involving Waldeyer's ring. Nodal recurrences are extremely uncommon (~5%) [108, 112, 113]. In the present era, elective nodal RT is not contemplatedunless there is a strong evidence to indicate a very high risk of nodal involvement (very bulky disease or primary lesion is in very close proximity to the nodes).

9.1 RT Dose Consideration for Solitary Plasmacytoma (SP)

There are no established guidelines for optimal radiation dose for SP's. A large multi-institutional study ($n = 258$) did not show a dose–response relationship beyond 30–35 Gy

[106]. However, it is a common practice to use a RT doses of 40–45 Gy [114]. Mendenhall et al. in a retrospective review of 81 patients reported a local control rate of 94% with 40 Gy or above, which compared with 69% for doses <40 Gy [115]. Studies have reported the futility of RT dose escalation (45–60 Gy) and have reported sporadic local failures at the local site even with doses of 50–60 Gy [105, 116]. A large retrospective study from Princess Margaret Hospital reported the lack of dose response relationship above 35 Gy [109] for tumors 5 cm (100% local control for SBP <5 cm). However, tumors >5 cm diameter had a response of only 38%. It was suggested that higher RT doses is required only for bulky tumors 5 cm or more in maximum diameter [109]. There is also some evidence that SEP is optimally controlled with a dose of 40 Gy or more [111, 117, 118].

RT Dose Practices at Tata Memorial Centre for Plasmacytomas

The following dose guidelines are followed (with dose /fraction of 1.8–2 Gy daily fractions)

- Smaller solitary bone plasmacytoma (<5 cm): definitive RT dose of 45 Gy
- Larger solitary bone plasmacytomas with extensive bone destruction (≥5 cm): RT doses of 50–54 Gy
- Solitary extramedullary plasmacytomas: total dose 45–50 Gy

10 Surgery for Multiple Myeloma

Surgical intervention in SPs is not commonly performed. Specific indications include stabilization of spine. Decompressive surgery is indicated in case of neurological compromise or a combination of the preceding situations.

Vertebroplasty is a commonly performed procedure in cases of structural instability due to myeloma. Vertebroplasty should be attempted in limited vertebral involvement and in the absence of spinal cord compression, which is an absolute contraindication for the above procedure.

11 Multiple Myeloma Palliation with Radiation Therapy

Osteolytic lesions are commonly observed at diagnosis in almost 70–80% of patients with MM [119, 120]. Common presentations include bone pain, pathologic fractures, and neurologic compromise such as spinal cord or nerve root compression, and cranial nerve deficits [121, 122]. RT in MM is for palliation. In case of compression fractures or impending fractures of weight bearing bones, RT should be considered only after surgical intervention as this would not only stabilize the spine/weight bearing bone but also relieve the patient of symptoms due to instability. RT alone has also been shown to be a very effective palliative treatment for patients with spinal cord compression. A retrospective study of 238 myeloma patients has shown excellent response rates (97%), local control (93% at 1 year and 82% at 2 years) and functional outcomes (64% of non-ambulatory patients regained the ability to walk) in patients treated with RT alone [123]. The role of RT in MM is to provide durable pain relief, ameliorate neurologic symptoms, promotes recalcification of bone, and improves quality of life.

In contrast to SP, where doses in the range of 40–54 Gy is required to obtain durable local control (≥85%), lower doses of RT are sufficient to obtain a clinical benefit in patients with symptomatic bony lesions from MM. A retrospective study investigated the most effective radiotherapy schedule in a large cohort of MM patients with spinal cord compression from vertebral body disease [124]. The study compared a short course (8 Gy in 1 fraction; 20 Gy in 5 fractions) to a longer course (30 Gy in 10 fractions, 37.5 Gy in 15 fractions, and 40 Gy in 20 fractions), with respect to improvement of functional outcome for at least 6 months or until death. The long course resulted in higher rates of improvement in motor function, when compared to short course both at 6 (67% vs 43%, $p = 0.043$) and 12 months (76% vs 40%, $p = 0.003$). Conversely, the functional outcomes were similar between the three long course schedules at the given time points. A randomized trial comparing 30 Gy in 10 fractions with 8 Gy in 1 fraction for symptomatic bone lesions in a large cohort of myeloma patients found similar response rates for pain relief but the quality of life improvement with RT was better in fractionated RT arm [125].

RT Dose Practices at Tata Memorial Centre for Palliative RT in Multiple Myeloma

- For bone lesions, where the goal is symptom relief: hypofractionated regimen with total dose of 8–33 Gy (e.g., 8 Gy in 1 fraction, 12 Gy in 2 weekly fractions, 20 Gy in 5 daily fractions, or 33 Gy in 11 daily fractions).
- For epidural disease with spinal cord compression, or a bulky mass, where durable local control is desired, 20 Gy in 5 or 33 Gy in 11 fractions with conformal RT.
- Tapering doses of dexamethasone is recommended for cases with nerve root or spinal cord compression to prevent pain flare (Dexamethasone 4 mg thrice daily to start with and then tapered down slowly).

11.1 Management Algorithm for Multiple Myeloma at TMC (Fig. 4)

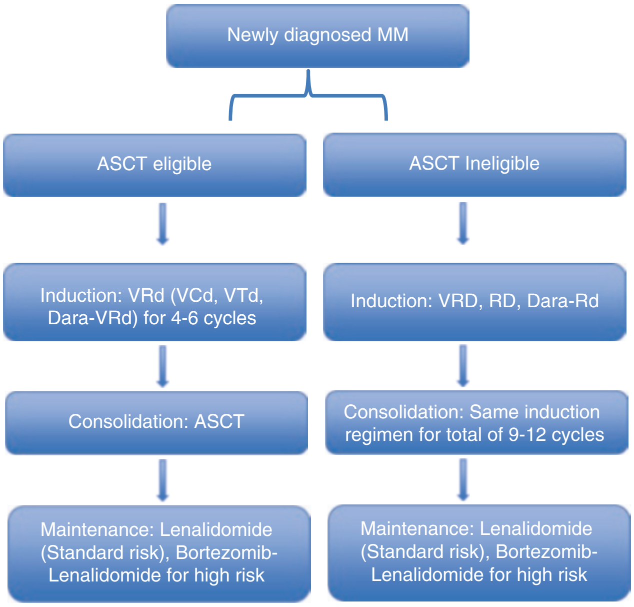
Newly diagnosed MM
ASCT eligible
ASCT Ineligible
Induction: VRd (VCd, VTd, Dara-VRd) for 4-6 cycles
Induction: VRD, RD, Dara-Rd
Consolidation: ASCT
Consolidation: Same induction regimen for total of 9-12 cycles
Maintenance: Lenalidomide (Standard risk), Bortezomib-Lenalidomide for high risk
Maintenance: Lenalidomide (Standard risk), Bortezomib-Lenalidomide for high risk

Fig. 4 Management algorithm for multiple myeloma at TMC

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Immunodeficiency-Associated Lymphoproliferative Disorders

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Abbreviations

ALPS	Autoimmune lymphoproliferative syndrome
AT	Ataxia-telangiectasia
BL	Burkitt lymphoma
cART	Combined antiretroviral therapy
CVID	Common variable immunodeficiency
DLBCL	Diffuse large B cell lymphoma
EBV	Epstein-Barr virus
HHV8/KSV	Human Herpes8/Kaposi sarcoma virus
HIgM	Hyper-IgM syndrome
HL	Hodgkin lymphoma
HSCT	Hematopoietic stem cell transplant
IBL	Immunoblastic
KHSV	Kaposi sarcoma associated human herpes virus
LPD	Lymphoproliferative disorder
MACS	Multicenter AIDS Cohort Study
MCD	Multicentric Castleman's disease
NBS	Nijmegen breakage syndrome
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PBL	Plasmablastic lymphomas
PCNSL	Primary central nervous lymphomas
PEL	Primary effusion lymphomas
PID	Primary immune deficiency
PTCL	Peripheral T-cell lymphoma
PTLD	Post-transplant lymphoproliferative disorders
RI	Reduction of immunosuppression
SCID	Severe combined immunodeficiency
SOT	Solid organ transplant
WAS	Wiskott-Aldrich syndrome
XLP	X-linked lymphoproliferative disease

The prevalence of immunodeficiency-associated lymphoproliferative disorders in India is mainly driven by HIV-associated lymphomas. However, with the increasing number of organ transplant centers, the incidence of post-transplant lymphoproliferative disorders is likely to rise.

Immunodeficiency-associated lymphoproliferative disorders (LPDs) are classified into the following broad groups, depending on the underlying immunodeficiency [1]:

- Lymphomas associated with human immunodeficiency virus (HIV) infection
- LPDs associated with primary immune disorders
- Post-transplant lymphoproliferative disorders (PTLD)
- Other iatrogenic immunodeficiency-associated LPDs

1 Lymphomas Associated with HIV Infection

1.1 Prevalence

Lymphoma continues to be a leading cause of cancer-related mortality in HIV patients even in the era of combined antiretroviral therapy (cART). The incidence of lymphoma amongst HIV patients is approximately 2% in the Western world [1, 2]. The estimated burden of HIV-infected patients in India is 2.1 million cases according to UNAIDS 2018 data with an incidence of 0.1 per 1000 population [3]. Non-Hodgkin lymphoma was the most common cancer accounting for 77 of 251 patients with HIV and cancer presenting at the Tata Memorial Hospital (TMH) between 2001 and 2005 [4]. Although there is no large data to confirm the prevalence of

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HIV-associated lymphoma in India, it is likely to be a major cause of mortality and morbidity in patients living with HIV and AIDS, as it is globally. In an autopsy study of HIV-positive patients from Mumbai, the incidence of non-Hodgkin lymphomas was 3% [5].

1.2 General Features of HIV-Associated Lymphomas

While Non-Hodgkin lymphomas (NHL) have been labeled as AIDS-defining illnesses since 1985, Hodgkin lymphoma (HL) is not considered an AIDS-defining illness, even though it occurs with increased frequency in HIV patients. Non-Hodgkin lymphoma (NHL) is 60 times more common in AIDS patients than in the general population [6]. Essentially, HIV-associated lymphomas are characterized by a high incidence of extra-nodal presentations, aggressive behavior, and increased association with Epstein-Barr virus (EBV) or Human Herpes8/Kaposi sarcoma virus (HHV8/KSV). Eighty percent of NHLs in AIDS patients are systemic NHL's while primary central nervous lymphomas (PCNSL) form 20% [7, 8]. Of the systemic lymphomas, 40% are diffuse large B cell lymphoma (DLBCL) and 30% each are formed by immunoblastic and Burkitt lymphoma. A drop in the incidence of PCNSL after the availability of cART therapy has been observed. The spectrum of HIV-associated lymphoma varies in different populations. The commonest type of lymphoma seen at our center is diffuse large B cell lymphoma (DLBCL) accounting for 50% and plasmablastic lymphoma accounting for 30% of HIV-associated lymphomas [9]. In a retrospective audit from Tata Memorial Centre conducted between 2000 to 2011, out of 265 HIV-associated lymphomas, 39% were DLBCL (including immunoblastic lymphoma), 45% were plasmablastic lymphomas (PBL), 10% were Burkitt lymphomas, 4% were unclassifiable, 1% was plasmacytoma and 1% had other tumor types (unpublished observations). A distinct absence of HHV8-related lymphomas or lymphoid proliferations was noted in this study which is in sync with the low prevalence of HHV8 in India.

1.3 Pathogenesis

The higher incidence of lymphomas in HIV and AIDS is believed to be due to the following.

- Chronic B cell stimulation and proliferation. It is now clear that the HIV virus is not directly involved in the transformation of B cells [8]. Dendritic histiocytes in the germinal center of lymphoid follicles serve as a sanctuary for HIV virus proliferation leading to chronic B cell stimulation and these stimulated B cells are prone to mutational changes. HIV stimulates monocytes and macrophages to produce IL6 a B cell differentiation factor that functions as an autocrine growth factor.
- Immunosuppression predisposes B cells to a genetic mutation. The nodes that exhibit florid follicular hyperplasia contain clonal B cell populations that are immortalized but not transformed. Lack of adequate immunity due to defective T cell function leads to failure of removal of hyper-stimulated clonal B cells that are genetically unstable and prone to develop translocations, especially in bcl6/cmyc.
- Susceptibility to infection by transforming viruses. EBV/HHV8 infection in HIV patients builds an oncogenic environment. EBV is capable of immortalizing B cells but may be insufficient by itself for tumor development. Likewise, HHV8/KSV is known to activate Cyclin D1 and some cell cycle proteins that can lead to the development of lymphomas indirectly [8].

Three factors determine what type of lymphoma occurs in an HIV-infected person and are also responsible for the heterogeneity of lymphomas in HIV [10]:

- The degree of immune deficiency in the host. The more preserved an immune status of a patient the more differentiated subtypes of lymphomas develop. Thus, Hodgkin lymphoma and diffuse large B cell lymphoma are common in patients on cART and higher CD4 counts while plasmablastic lymphomas occur in patients with severe immune deficiency.
- Coexistent viral infection and molecular pathways affected different ethnic groups. While HHV8 infection gives rise to primary effusion lymphomas (PEL) in severely immunodeficient patients, in populations where HHV8 seroprevalence is low (like India) plasmablastic lymphomas occur more commonly.
- The cell of origin is involved in the development. Depending on the stage at which the B cell development is affected the resultant tumor varies.

1.4 Histologic Classification of Lymphomas Associated with HIV Infection

HIV-associated B cell lymphomas express immunophenotypes similar to those expressed by lymphomas of comparable morphology occurring in immunocompetent individuals. A summary of these lymphomas is presented in Table 1.

1.4.1 Primary CNS Lymphoma (PCNSL) in HIV Patients

PCNSL is uncommon in HIV patients in India and one study quoted 1/56 PCNSL being HIV positive [11]. PCNSL in HIV-positive patients is associated with Epstein-Barr virus

(EBV), whereas EBV is rare in immunocompetent PCNSL patients. Pathologically PCNSL in immunocompetent and immunodeficient patients is similar and shows a centroblastic or large B cell morphology with the characteristic angiocentric pattern. Most PCNSLs (96%) are positive for multiple myeloma antigen 1 (MUM-1) (a marker of germinal center/early post-germinal center B cells), indicating a late germinal center (GC)/early post-germinal center stage of differentiation [12].

Table 1 Histological classification of lymphomas associated with HIV infection

Lymphomas also occurring in immunocompetent patients
• Burkitt lymphoma
• Diffuse large B-cell lymphoma including Primary CNS lymphoma
• Peripheral T-cell lymphoma (rare)
• Classic Hodgkin lymphoma
Lymphomas occurring more specifically in patients who are HIV patients
• Plasmablastic lymphoma
• HHV8 associated B cell lymphoid proliferations and lymphomas
Lymphomas occurring in other immunodeficiency states
• Polymorphic B-cell lymphoma

1.4.2 Diffuse Large B Cell Lymphoma (DLBCL) in HIV Patients

The heterogeneity of DLBCL in non-HIV patients is maintained even in AIDS patients. Amongst the unique morphology, the immunoblastic variant is the hallmark of AIDS-related DLBCL. DLBCLs containing >90% immunoblasts and usually exhibiting plasmacytoid features are classified as the immunoblastic (IBL) variants and 90% of these harbor an EBV infection.

In the AIDS malignancy consortium study, the relative proportion of germinal center DLBCLs was higher than in immunocompetent patients and the frequency of EBV in DLBCLs was not increased in AIDS patients [13]. However, in a study at our institute (unpublished observations) we observed that a third of HIV-associated lymphomas could not be classified as either germinal center or non-germinal center type. Similarly in a study that compared AIDS DLBCL with non-AIDS DLBCL, it was observed that while non-AIDS DLBCL clustered into the germinal center and activated B cell groups easily, AIDS DLBCL did not cluster similarly and showed profiles with overlapping features [14]. Morphologically most HIV-associated DLBL show a dominance of immunoblastic variants and show a high Mib1 index (Fig. 1a, b).

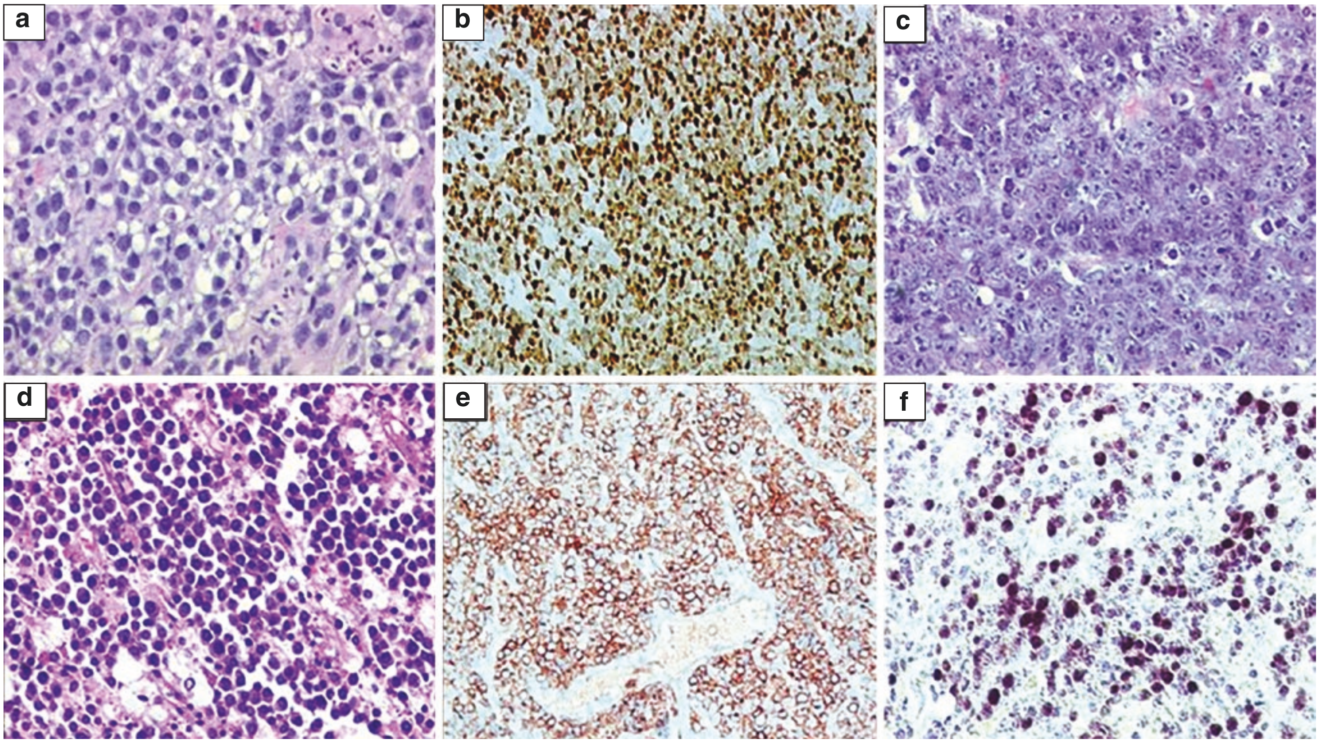

Fig. 1 Morphology of HIV-associated lymphomas. (**a**) Oral large B cell lymphoma with immunoblastic-appearing large cells (H&E 400). (**b**) MUM1 positivity in same (IP 200). (**c**) Plasmablastic lymphoma with blastic morphology (H&E 400). (**d**) Plasmablastic lymphoma myeloma-like (H&E 400). (**e**) CD138 staining in plasmablastic lymphoma (IP 200). (**f**) EBER in situ hybridization shows positive black nuclear staining (ISH 400)

1.4.3 Burkitt Lymphoma

Burkitt lymphoma (BL) is a germinal center tumor with a high proliferation index that needs to be treated with intensive regimens. While BL in immunocompetent patients has extranodal presentation, in HIV patients BL is often nodal in distribution. HIV-positive patients harboring BL are often young, do not usually carry a diagnosis of AIDS, and have fairly preserved CD4 counts [15]. Many AIDS-associated DLBCL show a high proliferative index and often it is not possible to differentiate BL from DLBCL. We have also come across a few Burkitt lymphomas with reduced CD20 expression in HIV patients with low CD4 counts and these pose a diagnostic challenge with plasmablastic lymphomas in these patients.

1.4.4 Polymorphic B Cell Lymphomas

Nador et al. described ten cases of lymphomas in AIDS patients which morphologically resemble polymorphic lymphoproliferation occurring in post-transplant patients [16]. Similar to post-transplant lymphoproliferative disorders PTLD these were characterized by a polymorphous lymphoid cell population exhibiting variable plasmacytic differentiation, cytologic atypia, epithelioid histiocytes, numbers of atypical immunoblasts, and focal coagulative necrosis. None of the patients had a history of severe opportunistic infections or Kaposi's sarcoma or carried a known diagnosis of AIDS at the time of presentation and had low CD4 counts. Improvement of CD4 counts resulted in regression in a few of them.

1.4.5 Plasmablastic Lymphoma (PBL)

This is a highly aggressive B-cell lymphoma with plasmacytic differentiation in HIV-positive patients which commonly affects extranodal sites like the oral cavity, gastrointestinal tract, and lymph nodes [17].

While the clinical spectrum of PBL is well elucidated the pathologic diagnosis has become complex. The vast majority of PBL cases are seen in patients with chronic HIV infection and low CD4 cell counts and cART is of value not only to treat but also to prevent PBL in HIV patients. Given these factors, it is not surprising that this unique lymphoma occurs commonly in Indian patients. Most cases of PBL present with either stage III or stage IV disease. EBV is detected in 74%. PBL is CD20 negative or weak positive; LCA, CD138, CD38, and MUM1 are positive and PAX5 is negative suggestive of post-germinal center immunophenotype. The histological spectrum of DLBCL with plasmablastic features has however widened to include subtypes, such as PBL of oral mucosa type, PBL with plasmacytic differentiation, classic primary effusion lymphoma (PEL), extracavitary/solid PEL or HHV8-associated DLBCL, and ALK-positive DLBCL. There are two histologic subtypes of PBL, one is a blastic type which mimics high-grade B cell lymphomas and the other is myeloma-like which mimics plasma cell neoplasm (Fig. 1c–e). Few DLBL in the HIV setting may show weak CD20 and negativity for PAX5 serves to distinguish PBL from CD20 low DLBL. In our experience, PBL in a non-immunocompromised setting is not common in India and in such cases, a plasmablastic plasmacytoma should be ruled out with a skeletal survey, serum electrophoresis, etc.

More recently, the MYC rearrangement, which is a characteristic of Burkitt's lymphoma (BL), and some DLBCL with very aggressive clinical behavior have been identified as the most common recurrent structural chromosomal alteration in PBL [18].

1.4.6 Primary Effusion Lymphomas (PEL)

Cesarman et al. in 1995 identified Kaposi sarcoma-associated human herpes virus (KHSV) DNA in a unique group of AIDS-associated lymphomas that primarily affected body cavities and presented with effusions [19]. Subsequently, the same team coined the term PEL or primary effusion lymphomas for these tumors. PEL forms 4% of all lymphomas in AIDS patients but has been reported in patients with other forms of immunodeficiency, in non-immunocompromised elderly patients, and in geographic areas with high KHSV prevalence. This subtype is not common in Indian patients just like Kaposi sarcoma, as the seroprevalence of HHV8 in India is low [20].

Microscopically PEL has morphologic features like immunoblastic lymphoma but the PEL cells have enormous size and prominent nucleoli. PEL also share most of their immunophenotype with plasmablastic lymphomas except for association with HHV8, clonal Ig rearrangements, and somatic hypermutations. Hence PEL are LCA positive (95%), showing the absence of B and T antigens, express activation marker CD30, EMA, and plasma cell markers CD138, CD38, and MUM1 with the expression of the KHSV latent protein LNA1. We have encountered intrasinusoidal EBV-associated-PEL-like lymphomas in our patient population (unpublished observation) indicating that PEL may be a morphologic pattern produced by both EBV and HHV8 viruses.

1.4.7 Large B Cell Lymphoma Arising in Multicentric Castleman's Disease (MCD) in HIV Patients

HHV8 is specifically associated with a variant of MCD with lambda light chain restricted KSV positive plasmablasts in the mantle zone of B cell follicles. These plasmablasts in MCD are large with moderate amphophilic cytoplasm and large vesicular nuclei with one or two prominent nucleoli and show CD20, LNA 1, CD138 positivity and light chain restriction but are negative for CD30. Though MCD is known in HIV-positive Indian patients at our institute no HHV8 positivity has been noted (unpublished observations).

1.4.8 Peripheral T Cell Lymphoma

Data on HIV-associated PTCL are largely limited to case reports and small case series. PTCL is associated with low CD4 counts and poor survival. While PTCL-NOS and ALK-negative ALCL morphology are the most common amongst PTCL, the response rate is similar to immunocompetent patients with PTCL and ranges from 50% to 70%. While diagnosing a PTCL in untreated HIV patients with poor immune status pathologists should remember that clonal CD8-positive reactive proliferations that resolve after HAART therapy are known. In our study of NHL in HIV patients most of the atypical T cell proliferations though clonal, turned out to be reactive and reversed after cART therapy and only one pediatric patient died due to CD8-positive T cell lymphoma.

1.4.9 Hodgkin Lymphoma (HL) in HIV Patients

HL represents the most common type of non-AIDS-defining tumor that occurs in the HIV-infected population. After a 12-year follow-up, the Multicenter AIDS Cohort Study (MACS) found the relative risk for HL in HIV-positive individuals versus the US general population to be 7.0. HIV-HL patients have widespread disease at presentation, high incidence of systemic “B” symptoms with frequent involvement of extranodal sites like bone marrow, liver, and spleen, and non-contiguous spread of the tumor. In HIV setting primary marrow Hodgkin’s lymphoma is also known to occur. HL occurring in HIV-infected individuals exhibits pathologic features different from those of HL in the general population including a higher incidence of unfavorable histologic subtypes like mixed cellularity (40–100%) and lymphocyte depleted (20%), and a relatively low prevalence of the nodular sclerosis and lymphocyte predominant subtypes [21]. HL in the HIV setting displays a distinct cellular background, including the presence of a fibrohistiocytoid stromal cell proliferation in the involved lymph nodes. Another morphological characteristic is the abundance of Reed Sternberg cells, mimicking ALCL. A large majority of HIV-related Hodgkin lymphoma (80–100%) are linked pathogenetically to EBV as opposed to HIV-negative HL.

Tables 2 and 3 present the differential diagnosis of CD20-positive and CD20-negative lymphomas in HIV.

1.5 Clinical Features and Approach to Patients with HIV-Associated Lymphomas

Lymphoma may be the first presentation in HIV patients. At our center, lymphoma was the initial manifestation of HIV and led to the detection of HIV at presentation in 21 out of 42 patients (50%) [9]. It is recommended that HIV should be tested in all individuals who present with lymphoma (both Hodgkin and non-Hodgkin). Patients usually present with rapidly increasing mass (nodal or extranodal) along with B symptoms which include fever, weight loss, and night sweats. Oral or facial masses are common presentations, especially

Table 2 Differential diagnosis in CD20-positive AIDS-related lymphomas

Diffuse large B cell germinal center vs. Burkitt		Diffuse large B cell (immunoblastic) vs. plasmablastic	
Large to intermediate-size cells	Intermediate-size cells	Nuclei have a single prominent nucleolus	Nuclei in blastic have a prominent nucleolus
Pleomorphic cells	Monomorphic	Cell cytoplasm pale eosinophilic	Cell cytoplasm plasmacytoid and amphophilic
EBV latency varies	EBV latency I pattern EBER+, occasionallyEBNA1+,LMP1−/EBNA2−	EBER in 30% of tumors Variable latency	EBER in 80% tumors-latency I
Ki67 variable but less likely 100%	Ki67—100%	CD20 variable	CD20 is always focal, never strong positive
Molecular genetics: complex rearrangements including MYC may be seen	Molecular genetics: MYC rearrangements without other rearrangements	IgH gene rearrangements seen	IgH gene rearrangements absent

Table 3 Differential diagnosis of CD20-negative AIDS-related non-Hodgkins lymphomas

Features	Plasmablastic lymphoma	Primary effusion lymphoma	Immunoblastic DLBL
Morphology	Plasmacytoid cells	Immunoblastic or anaplastic cells	Immunoblastic cells
Immunohistochemistry	LCA weak +, CD20 (1–2%), CD138/MUM1 (90%), PAX5 negative EMA (42.5%)	LCA weak +, CD20 (13%), CD138/MUM1 (40%) EMA (70.0%), PAX5 negative	LCA+/−, CD20(+/−), CD138/MUM1+, EMA negative, PAX5 +
EBER-ISH	80% positive	Variably positive	Variably positive
EBV-LMP1	Negative	Negative	Positive
HHV8	Absent	Always present	Absent

of plasmablastic lymphoma in HIV patients. Extranodal involvement of the GI tract, liver, and CNS is more common than in non-HIV patients with lymphoma.

Initial workup should include apart from an HIV test, a CD4 count, and HIV viral load. Renal function, liver function tests, and lactate dehydrogenase (LDH) must also be done. Imaging should ideally include an 18 FDG Positron emission tomography (PET) scan. In case a facility for a PET scan is not available, contrast-enhanced CT scan may be done. CSF cytology to rule out CNS involvement in the case of NHL is mandatory. Tests must also be included to rule out concurrent hepatitis B (HBsAg, core antibody tests, and if required HBV viral load) and hepatitis C infection. Patients must undergo a complete physical examination to look for signs and symptoms of other opportunistic infections such as oropharyngeal candidiasis, tuberculosis other venereal diseases, which may be present simultaneously. An excision biopsy of the lymph nodal mass should be ideally performed. If this is not possible, then a core biopsy or incisional biopsy may be done.

1.6 Treatment

1.6.1 Concurrent cART

Over the last three decades, there has been a significant and dramatic improvement in the overall survival of HIV-associated lymphomas. Apart from better chemotherapy, one of the key factors which have led to this is the use of cART. The use of cART has led to a decrease in the incidence of DLBCL and PCNSL with an increase in the incidence of good prognostic lymphomas such as Hodgkin and Burkitt lymphoma [22]. Although there is no randomized trial comparing chemotherapy with and without cART to establish its effectiveness in HIV-associated lymphomas, there is substantial evidence that cART has improved the survival of HIV patients by improving immunity and decreasing opportunistic infections over the last three decades. Phase 2 data suggest chemotherapy can be combined with cART safely; however, pharmacokinetic interactions especially with cyclophosphamide and drugs such as ritonavir (protease inhibitor) [23]. Also, zidovudine needs to be avoided in view of potential cytopenias when combined with chemotherapy. However, it is not absolutely essential to start or continue cART when giving chemotherapy. Few studies using infusional EPOCH regimens have shown complete remission rates of more than 70% without the use of concomitant cART [24, 25].

1.6.2 Combination Chemotherapy

The presentation of HIV-associated lymphoma may vary from a severely immunocompromised individual to a fit individual with lymphoma. Therapy with curative intent is indicated in all patients with HIV and lymphoid malignancies including in patients with poor performance status as this may be due to malignancy per se or due to opportunistic infections which may improve with supportive care.

1.7 Treatment of DLBCL

Combination chemotherapy with a standard CHOP regimen has been the standard of care for DLBCL in non-HIV settings and has also been used in HIV-positive patients. A randomized trial comparing R CHOP and CHOP in a population of 150 patients with HIV lymphomas (80% of whom had DLBCL, 8% had BL and 4% had other NHL) showed an increase in infection-related mortality in the R CHOP arm (14% vs. 2% in CHOP arm) although the CR rates were much higher in R CHOP arm. However, this increased mortality was mainly seen in those patients who had a CD4 of less than 50 cells/mm^3 [26]. Subsequent phase II studies combining Rituximab with CHOP in HIV positive population showed complete remission (CR) rates of 77% and 2 year overall survival (OS) rates of 75%. These studies included patients with CD4 counts of more than 100 and those mainly with DLBCL, Burkitt lymphoma, and very few patients with plasmablastic and immunoblastic lymphoma. Antiretroviral therapy was also used concurrently. There was no increase in infection-related deaths in this study confirming that R may be safely combined with chemotherapy in patients who have a CD4 >100 [27]. Multiple subsequent trials have safely combined R with chemotherapy regimens in HIV-positive patients.

Infusional dose-escalated EPOCH regimens with or without rituximab have also shown excellent response rates in HIV-positive populations with non-Hodgkin lymphoma [24, 28]. Other regimens such as R CDE also have shown response rates of 70% [29].

Dunleavy and colleagues have further shown that reduction in a number of cycles of EPOCH is possible in combination with dose-dense rituximab (EPOCH RR) without compromising the efficacy of the regimen. In this study, Rituximab was given on day 1 and day 5 along with the 96-h infusional EPOCH regimen in each cycle. A minimum of 3 and maximum 6 cycles were given. A PET scan was done after the second cycle and if not in complete remission was done after each subsequent cycle. Chemotherapy was continued up to 1 cycle beyond the achievement of complete response. The number of EPOCH cycles could be reduced to 3 in 79% of the patients with a progression-free survival rate of >80% at 5 years [25].

Although there are multiple regimens that can be used in HIV-associated DLBCL these are not compared in randomized controlled trials. These regimens use different drugs and different dosing schedules. Few of these regimens have omitted concurrent use of cART and hence their outcomes cannot be compared. However, a meta-analysis using pooled data

Table 4 Summary of different regimens used in treating HIV-associated NHL

Regimen used	Histology included (%)	Median CD4 at baseline (cells/mm^3)	Concomitant use of cART (yes/no)	Complete response rates	Progression-free survival rate	Overall survival rate	Reference
R CHOP (phase II)	DLBCL (70%) IBL (3%) BL (26%) PBL (1%)	172	Yes	76%	69% at 2 years	75% at 2 years	Boué et al. [27]
DA EPOCH	DLBCL (79%) BL (18%)	198	No (deferred till completion of chemotherapy)	74%	73% at 4 years	60% at 4 years	Little et al. [24]
R DA EPOCH (concurrent arm)	DLBCL (79%) BL (21%)	190	Yes, however at the physicians discretion	73%	66% at 2 years	70% at 2 years	Sparano et al. [28]
EPOCH RR (short course)	DLBCL (100%)	208	No	91%	68% at 5 years	84% at 5 years	Dunleavy et al. [25]
EPOCH RR (short course)	BL (100%)	322	No	100%	95% at 6 years	100% at 6 years	Dunleavy et al. [30]

DLBCL diffuse large B cell lymphoma, *BL* Burkitt lymphoma, *PBL* plasmablastic lymphoma, *IBL* immunoblastic lymphoma

from 19 trials with 1546 patients has shown that infusional regimens (EPOCH) led to significant improvement of OS. This study also showed that the use of concurrent cART led to significantly improved CR rates with a trend of improvement in OS [30].

Infusional regimens may be a better choice of therapy whenever feasible-keeping in mind that these regimens are cost-intensive and need substantial supportive care which may preclude their use in resource-limited settings in our country.

Table 4 compares the different regimens used in treating HIV-associated NHL.

1.8 Treatment of Burkitt Lymphoma

Most trials of HIV-associated lymphomas include mainly patients with DLBCL because it is the most common histology and has relatively fewer patients with BL. Chemotherapy with a CHOP regimen in HIV patients with BL has led to poor outcomes. Dose-escalated EPOCH regimens have shown improved outcomes with CR rates of 70% [28]. The use of dose-dense rituximab (EPOCH RR) in patients with BL has also shown a OS rate of 92% at a median follow-up of 73 months in a small cohort of 13 immunocompromised patients [31].

1.9 Treatment of Hodgkin Lymphoma

The treatment outcomes of HL in HIV-positive patients are comparable to those with HL in general. Patients with HIV tend to have more B symptoms, extranodal presentations, and advanced stage. The standard treatment for HIV-associated HL is using an ABVD regimen. The data on the use of ABVD regimens in HIV-positive patients is limited to small studies with few patient numbers. The largest study is from Spain, which included 62 patients of HIV with Hodgkin lymphoma. In this retrospective study conducted between 1995 and 2006, patients received 6–8 cycles of standard ABVD along with cART and growth factors. All patients had advanced disease (Stage III/IV). Five-year OS probability was 76% after a median of 47 months of follow-up [32].

Risk-adapted therapy has also been studied prospectively in a cohort of 108 patients. Patients of early favorable HL receiving 4 cycles of ABVD and 30 Gy involved field radiation (IFRT). Those with early unfavorable HL received either 4 cycles of ABVD and IFRT or 4 cycles of BEACOPP and those with advanced disease received 6–8 cycles of BEACOPP. All patients with advanced HIV disease (CD4 <50, poor performance status, and AIDS-related opportunistic infections) received ABVD only. The CR rates for those with early favorable, early unfavorable, and advanced-stage HL were 96%, 100%, and 86%, respectively. The two-year OS rate was 90.7% in the entire cohort and 95.7%, 100%, and 86.6% in early favorable, early unfavorable and advanced-stage HL respectively [33].

However, there were 7% treatment-related mortality and a higher incidence of grade 3–4 hematologic toxicities in advanced-stage disease, indicating that careful selection of patients is required before planning BEACOPP in HIV-associated HL.

1.10 Treatment of Other Lymphomas

Plasmablastic lymphoma is seen in patients with advanced HIV disease and usually has poor performance status. The data for the management of patients with plasmablastic lymphoma is limited. The outcomes of PBL are poor with CHOP-based therapy. Infusional regimens with DA EPOCH have shown slightly better outcomes. However median survival is still around 9 to 10 months [34]. Primary CNS lymphoma is almost always seen in patients with CD4 <50/mm^3. It is an EBV-associated malignancy and carries an extremely poor prognosis. The optimal treatment is not known. They should be enrolled in clinical trials as far as possible. Radiation therapy to the brain with a focal boost may be used. The use of cART has improved the outcomes in both of these malignancies and must be started upfront for these patients.

1.11 Supportive Care in HIV-Associated Lymphomas

Apart from chemotherapy and cART, another reason for the improvement in survival in patients with HIV-associated lymphomas is the overall improvement in supportive care. The use of prophylactic cotrimoxazole for preventing Pneumocystis Jiroveci infection and azithromycin weekly for Mycobacterium avium infection have led to a decrease in mortality due to these infections. It is important to look for and treat these opportunistic infections at the time of diagnosis and these should be managed simultaneously with the lymphoma treatment.

1.12 CNS Prophylaxis

HIV-associated NHLs have significant involvement in extranodal sites and are at a high risk for CNS disease at presentation and relapse [25]. All patients should receive intrathecal methotrexate with or without cytarabine. Usually, intrathecal injections are given twice weekly till 2 weeks after clearance of CSF followed by weekly for 6 weeks and then monthly for 6 months [25, 31].

2 LPDS Associated with Primary Immune Disorders

Primary immune disorders (PID) are a heterogeneous group of inherited disorders associated with defective immunity rendering a patient susceptible to different viral infections and malignancies. These usually present in the pediatric age group with the exception of common variable immunodeficiency (CVID) which may present in adolescents or young adults.

2.1 Prevalence

The age-specific mortality due to cancer in patients of PID is 10–200 times the general population; however, as PIDs are very rare disorders, they account for only 2% of pediatric lymphomas [35]. The prevalence of primary immune deficiency (PID) in India is statistically estimated to be around 1 million. However, the exact incidence of LPD associated with primary immune disorders is not known. This is due to a lack of diagnostic modalities and awareness [36].

PIDs most commonly associated with LPDs include ataxia-telangiectasia (AT), common variable immunodeficiency (CVID), severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome (WAS), X-linked lymphoproliferative disease (XLP), Nijmegen breakage syndrome (NBS), hyper-IgM syndrome (HIgM), and autoimmune lymphoproliferative syndrome (ALPS).

2.2 Pathogenesis

PIDs are all associated with poor T-cell function which is responsible for EBV viral proliferation.

Following primary infection, EBV is incorporated in the DNA of the host where it undergoes replication and transformation, especially in circulating B cells. The virus remains in a state of latency and its expansion is controlled by specific cytotoxic T cells. Inhibition of T cell function in these patients due to the PID promotes the proliferation of EBV which expresses BCRF 1 and 2 which helps these cells escape immune control. There is also an increase in the expression of LMP1 and 2 proteins which leads to cell proliferation and escape from apoptosis [1].

2.3 Clinical Features and Management

Most patients have a diagnosis of PID established due to other presenting features and due to recurrent infections in childhood. However lymphoproliferative disorders may be the initial presenting feature in ALPS and XLP. The morphology and immunophenotypes of the lymphomas associated with PID do not differ from those seen in the immunocompetent counterpart. DLBCL is the most common type of lymphoma seen in PIDs in general [37]. Classic HL, BL, and peripheral T-cell lymphoma (PTCL) can also occur. In some disorders like AT and NBS, T-cell lymphomas are more commonly seen than B-cell lymphomas.

Management of these children with PID-induced lymphomas is difficult and the treatments have to be individualized keeping in mind the nature of immunodeficiency and the presence of opportunistic infections which may be worsened by intensive chemotherapy. Allogenic stem cell transplant has been used to treat some of these patients successfully especially those with WAS, SCID, WAS, and HlgM [38, 39].

3 Post-transplant Lymphoproliferative Disorders (PTLD)

These lymphoproliferative disorders specifically occur post solid organ or hematopoietic stem cell transplant. The cumulative incidence of PTLD is low (0.2–1.1%) and mainly consists of B cell proliferative disorders. PTLD has been rarely reported in India, however with an increasing number of organ transplant centers and an increasing number of organ transplants being performed, it is likely to rise.

3.1 Classification

PTLDs are a group of heterogeneous disorders. The current histologic classification of PTLDs is as follows and depends on histology, presence of EBV, and clonality [1]:

1. Non-destructive PTLDs
    (a) Plasmacytic hyperplasia
    (b) Infectious mononucleosis
    (c) Florid follicular hyperplasia
2. Polymorphic PTLD
3. Monomorphic PTLDs (classified according to the lymphoma they resemble)
    (a) B-cell neoplasms: Diffuse large B-cell lymphoma, Burkitt lymphoma, plasma cell myeloma, plasmacytoma, and others
    (b) T-cell neoplasms: Peripheral T-cell lymphoma NOS, hepatosplenic T-cell lymphoma, and others
4. Classic Hodgkin lymphoma PTLD

3.2 Etiology

PTLD is associated with EBV infection, and similar to the pathogenesis of PID-induced lymphomas they occur due to deficient immunosurveillance and proliferation of EBV. EBV induces monoclonal and infrequently polyclonal B-cell or monoclonal T-cell.

3.3 Incidence

In post-hematopoietic stem cell transplant (HSCT), EBV proliferation and PTLD usually occur early within 1 year of transplant and the incidence of PTLD at 10 years is 1–2% [40]. The incidence post-solid organ transplant (SOT) varies according to the organ—it is highest after heart and lung transplant (6%) and is lower after other SOT (1–2% after kidney and liver transplants). The incidence is also significantly higher in children as compared to adults [41].

3.4 Clinical Features

These usually present with the involvement of lymph nodes. Extranodal involvement of the lungs, liver, skin, and GI tract is also common, and almost any site of the body may be involved. CNS involvement is uncommon. PTLD involving allograft has also been described post solid organ transplant and usually occurs in early onset PTLDs and is most common post lung transplants. Tonsillar involvement may be seen in non-destructive PTLDs. Widespread involvement in multiple organs and lymph nodes may be seen post HSCT.

3.5 Prognostic Factors

PTLDs carry a high mortality rate of 50% [42]. This has improved with newer modalities of treatment such as rituximab and EBV-specific T-cell therapy. High LDH, extranodal, multiorgan involvement, bulky disease, and advanced-stage, absence of response to reduction of immunosuppression (RI) are a few of the factors that have been associated with poor survival in some studies.

3.6 Management

Reduction of immunosuppression (RI) is the first and most important intervention that is done in the management of PTLD. Some, especially non-destructive PTLD may regress completely with RI. These lesions carry excellent prognosis, especially in children provided there is no acute or chronic graft rejection that is precipitated by RI. A large proportion of polymorphic PTLD and most monomorphic PTLD would not regress with RI alone and requires further intervention.

Treatment with Rituximab with or without chemotherapy is the standard treatment of PTLD. There is no large data comparing regimens. In a prospective open-label phase 2 trial of 70 post-SOT PTLD patients who had not responded to RI were treated sequentially with weekly rituximab (375 mg/m^2) followed by 4 cycles of 3 weekly CHOP led to median OS of 6 years [43].

In post-HSCT setting monitoring of EBV—especially in high-risk patients (T-cell-depleted transplants, mismatched transplants, and use of ATG) weekly monitoring of EBV viral load and pre-emptive treatment with rituximab before development of lymph nodes or mass lesions has been found to reduce mortality to 0% as compared to 26% in historic controls [44]. Newer modalities like EBV-specific T lymphocyte infusion has shown promising results, however, this is not easily available, especially in developing countries.

Immunodeficiency-associated lymphoproliferative disorders form a significant minority of lymphomas seen in clinical practice. Although prognosis in these disorders is still inferior compared to lymphomas in the general population, interventions like the use of cART, monoclonal antibodies, and infusional combinational chemotherapy regimens have dramatically improved the prognosis and long-term survival.

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Histiocytic and Dendritic Cell Neoplasms

Sridhar Epari and Gaurav Narula

Abbreviations

APC	Antigen-presenting cell
BCH	Benign cephalic histiocytosis
BPDCN	Blastic PDC neoplasm
COO	Cell-of-origin
DCs	Dendritic cells
DIDC	Dermal/interstitial dendritic cell
ECD	Erdheim–Chester disease
FDC	Follicular dendritic cells
FDCS	Follicular dendritic cell sarcoma
FRCT	Fibroblastic reticular cell tumor
GEH	Generalized eruptive histiocytosis
HS	Histiocytic sarcoma
IDC	Interdigitating dendritic cell
IDCS	Interdigitating dendritic cell sarcoma
JXG	Disseminated juvenile xanthogranuloma
LC	Langerhans cell
LCH	Langerhans cell histiocytosis
LCS	Langerhans cell sarcoma
MAPK	Mitogen-activated protein kinase
PDC	Plasmacytoid dendritic cells
PNH	Progressive nodular histiocytosis
RDD	Rosai–Dorfman/Rosai–Dorfman–Destombes disease
SHML	Sinus histiocytosis with massive lymphadenopathy
SRH	Solitary reticulohistiocytoma
XG	Xanthogranuloma

1 Introduction

Histiocytic disorders (histiocytoses) are rare lesions, derived from mononuclear phagocytic cells, macrophages and dendritic cells (DCs). DCs, monocytes and macrophages are members of the mononuclear phagocyte system with a distinctive immunophenotypic expression (Table 1), whereas a histiocyte is referred for macrophages in tissue [1].

Table 1 Expression of immunohistochemical markers for histiocyte/macrophage and dendritic cells

Marker	LC	IDC	FDC	PDC	M	DIDC
CD1a	++	–	–	–	–	–
CD4	+	+	+	+	+	+/–
CD21	–	–	++	–	–	–
CD35	–	–	++	–	–	–
CD68	+/–	+/–	–	++	++	+
CD123	–	–	–	++	–	–
CD163	–	–	–	–	++	–
Factor XIIIa	–	–	+/–	–	–/+	++
Fascin	–	++	+/++	–	–/+	+
Langerin	++	–	–	–	–	–
Lysozyme	+/–	–	–	–	+	–
S-100	++	++	+/–	–	+/–	+/–
TCL-1	–	–	–	+	–	–

Abbreviations: *LC* Langerhans cell, *IDC* interdigitating dendritic cell, *FDC* follicular dendritic cell, *PDC* plasmacytoid dendritic cell, *M* macrophage, *DIDC* dermal/interstitial dendritic cell

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2 Histiocytes/Macrophages

The histiocytes/macrophages are derived from peripheral blood monocytes and play the role of scavenging of apoptotic cells, necrotic debris and pathogens [2]. They migrate to the tissue and acquire the phagocytic potential in tissue and is one of an integral component of the native innate arm immune system with pro/anti-inflammatory effects, as well as in particulate removal and tissue reconstitution [2]. This phagocytosing macrophages show increased expression of lysosomal enzymes (can be detected histochemically—nonspecific esterases and acid phosphatase stains).

3 Dendritic Cells

Dendritic cells (DCs) play a role in activating naive T-lymphocytes by playing a role in antigen presentation in conjunction with major histocompatibility complex molecules. Based on histogenetic origins, they can be myeloid or stromal derived with different cellular subsets and shows differential immunophenotypic findings (see Table 1) [3].

3.1 Myeloid-Derived DCs

The functional spectrum and activational status of dendritic cells (DCs) or antigen-presenting cells (APCs) is wide and variable depending upon the tissue of its location and its functional role in that tissue. Thus, no single marker identifies all dendritic cell subsets (see Table 1) [4]. Some of the special types are listed below:

- Langerhans cells are specialized DCs, seen in mucosa and skin; where it plays a role of antigen presentation to T-lymphoid cells and subsequently migrate to the regional lymph node through lymphatics. Immunophenotypically, these cells express CD1a and show ultrastructural Birbeck granules (see Table 1).
- Interdigitating dendritic cells: Lymph nodal paracortical dendritic cells, probably derived from the Langerhans cell. This classic dendritic cell lineage is considered to be the cell-of-origin (COO) for Langerhans cell histiocytosis/sarcoma and also of interdigitating dendritic cell sarcoma [5].
- Dermal/interstitial dendritic cells—found in the soft tissue, dermis and most organs, which can be increased in some inflammatory states.
- Plasmacytoid dendritic cells (PDCs) are a distinct type of dendritic cells, currently considered as COO for the blastic PDC neoplasm. Its histogenetic origin is controversial and is classified with the myelomonocytic lineage group [6].

3.2 Stromal-Derived DCs

- Follicular dendritic cells (FDCs) play the role of APCs to B-lymphoid cells within lymphoid follicles (both primary and secondary). They are closely related to bone marrow stromal myofibroblast-like cells. They are nonmigrating and form a stable cell-to-cell meshwork within the germinal center of the follicle [7].
- Fibroblastic reticular cells, on the other hand, ensheath the postcapillary venules and also help in maintaining lymphoid integrity through cytokines. They are also of mesenchymal origin and show myofibroblastic phenotype [8].

4 Spectrum of Histiocytoses

The Working group of the Histiocyte Society, in 2016, categorized histiocytic disorders into five groups based on clinical, radiographical, histological, immunophenotypical, genetic, and/or molecular features (Table 2) [9].

1. L (Langerhans) group—Langerhans cell histiocytosis (LCH), indeterminate cell histiocytosis (ICH), Erdheim–Chester disease (ECD), mixed LCH/ECD.

Table 2 Recent classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

Histiocyte Society	WHO classification of tumors of hematopoietic and lymphoid tissues	WHO classification of skin tumors
• **L group** LCH, ICH, ECD, mixed LCH/ECD • **C group (non-LCH of skin and mucosa)** Xanthogranuloma family (includes JXG) Non-xanthogranuloma family (includes MRH) • **M group** HS, LCS, IDCS, IC sarcoma • **R group** RDD (classical and variants) • **H group** HLH (primary and secondary)	• HS • LCH and LCS • IDCT • IDCS • FDCS • DJXG • ECD	• LCH • IDCH/IDCT • RDD • JXG • ECD • MRH

Abbreviations: *DJXG* disseminated juvenile xanthogranuloma, *ECD* Erdheim–Chester disease, *FDCS* follicular dendritic cell sarcoma, *HLH* hemophagocytic lymphohistiocytosis, *HS* histiocytic sarcoma, *IC* indeterminate cell, *ICH* IC histiocytosis, *IDCH/IDCT* indeterminate dendritic cell histiocytosis/tumor, *IDCS* interdigitating dendritic cell sarcoma, *JXG* juvenile xanthogranuloma, *LCH* Langerhans cell histiocytosis, *LCS* Langerhans cell sarcoma, *MRH* multicentric reticulohistiocytosis, *RDD* Rosai–Dorfman–Destombes disease

2. C (Cutaneous) group:
    (a) Cutaneous non-LCH: xanthogranuloma (XG) family (juvenile xanthogranuloma, adult xanthogranuloma, solitary reticulohistiocytoma [SRH], benign cephalic histiocytosis [BCH], generalized eruptive histiocytosis [GEH] and progressive nodular histiocytosis [PNH]); non-XG (cutaneous Rosai–Dorfman disease, NXG, others, NOS).
    (b) Cutaneous non-LCH with a major systemic component.
3. R (Rosai–Dorfman–Destombes) group—sporadic RDD (classical, i.e., nodal; extranodal, neoplasia or immune disease-associated and unclassified) and familial RDD.
4. M (Malignant) group—primary (malignant tumors of histiocytic phenotype, interdigitating, Langerhans, indeterminate cell) and secondary.
5. H (Hemophagocytic) group: primary (inherited conditions), secondary and of unknown/uncertain origin.

5 Histiocytic and Dendritic Cell Neoplasms

Of the above listed histiocytic lesions, the entities that are characterized by clonal molecular abnormalities leading to proliferation of the cells are considered neoplastic. The current 2017 WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues grouped all neoplasms that exhibit stable and constant morphological, phenotypic, and ultrastructural characteristics of terminally differentiated histiocytic and dendritic cells under this category (Tables 2 and 3) [10]. In keeping with this notion, the blastoid plasmacytoid cell neoplasm (as it stems from a cell that acquires terminal differentiation and dendritic appearance following activation) is not considered in this group of histiocytic and dendritic cell and rather is included in the group of acute myeloid leukemia-related neoplasms. Thus, the current 2017 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, includes the following entities as histiocytic and dendritic cell neoplasms:

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma, follicular dendritic cell sarcoma, fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma
- Erdheim–Chester disease

RDD was not included under of histiocytic and dendritic cell neoplasms in the 2017 WHO classification of Tumours of Haematopoietic and Lymphoid Tissues, as it was previously perceived to be a nonclonal proliferation. However, recent evidence has shown the clonal nature of at least a subset of cases of RDD, which should be considered as neoplastic and is likely to get updated in the upcoming newer edition of WHO classification. In this chapter, RDD has been listed along with the other above listed entities.

Table 3 Commonly used immunohistochemical markers in the diagnosis of histiocytic and dendritic cell tumors

Antigen	Main reactivity in normal cells	Diagnostic utility
CD1a	LC Dermal DC (subset) IDC (subset)	Required for diagnosis of LCH/LCS and IDCT Positivity excludes IDCS
CD11c	H/M Most DC (most epidermal LC are negative)	Sensitive marker for most H/M and DC neoplasms
CD14	H/M	H/M-derived tumors (less frequent than in monocytic leukemias)
CD68	H/M PDC	Diffuse granular cytoplasmic reactivity in most H/M-derived tumors; variable in DC neoplasms Poor specificity (expressed by many nonhematopoietic tumors, including melanoma)
CD123	PDC Activated macrophages; nodal sinus lining cells high endothelial venule endothelium	High sensitivity and specificity for BPDCN Can be expressed in LCH and in H/M-derived tumors
CD163	H/M	Best markers for H/M--derived tumors (high sensitivity and specificity)
Langerin (CD207)	LC IDC (subset)	Defining LCH/LCS Exclude IDCS
BDCA2/ CD303	PDC	High specificity for BPDCN
Lysozyme	H/M	Often expressed in H/M-derived tumors, but poor specificity
S-100 protein	LC, IDC, activated H/M	Required for of LCH/LCS, IDCT, IDCS and RDD diagnosis Expressed in variable number of cells in various H/M tumors

Abbreviations: *BPDCN* blastic PDC neoplasm, *DC* dendritic cells, *H/M* histiocytes/macrophages, *IDC* interdigitating dendritic cells, *IDCT* indeterminate dendritic cell tumor, *IDCS* interdigitating dendritic cell sarcoma, *LC* Langerhans cells, *LCH* Langerhans cell histiocytosis, *LCS* Langerhans cell sarcoma, *PDC* plasmacytoid dendritic cells, *RDD* Rosai–Dorfman–Destombes disease

6 Histiocytic Sarcoma (HS)

Histiocytic sarcoma (HS) is a malignant tumor of cells with immunohistomorphological features of mature histiocytes (tissue macrophages). However, proliferations associated with monocytic leukemia should not be included in this category. They show mild male preponderance and commonly presents as solitary extranodal mass in adults (median age: 52 years) at sites like soft tissue, skin, gastrointestinal tract and bones, usually associated with systemic symptoms. Rarely can involve lymph nodes and still rarely as disseminated disease (then it should be termed as malignant histiocytosis rather than HS) [11].

Diagnosis is essentially made on histology, which shows relative dyscohesive sheets of large cells of varying shapes with abundant eosinophilic to pale eosinophilic (sometimes with cytoplasmic vacuolation; xanthomatous-like) cytoplasm, significant nuclear atypia and mitoses; in cases of lymph nodes and spleen—usually exhibits sinusoidal growth pattern; erythro/hemophagocytosis by tumor cells can be prominent (Fig. 1). Commonly admixed inflammatory cells—lymphocytes, neutrophils, eosinophils and plasma cells—are noted. Immunohistochemically, the HS cells show positivity of histiocyte/macrophage-associated markers CD163, CD11c, CD14, CD68 and lysozyme. S100-protein is positive in almost 50% of cases and may indicate a co-occurring LC sarcoma component. However, it has to be noted they should be negative for markers of other high-grade hematolymphoid and nonhematolymphoid (mesenchymal sarcomatous) neoplasms.

BRAF mutations (V600E and other variants), activating mutations of RAS/RAF/MEK/ERK, RAS/MAPK and PI3K-AKT-MTOR and loss of the *CDKN2A* gene are frequent genetic alterations [12]. Some cases are shown to be associated with prior or metachronous clonally unrelated low-grade follicular lymphoma, the pathobiology of the same is uncertain.

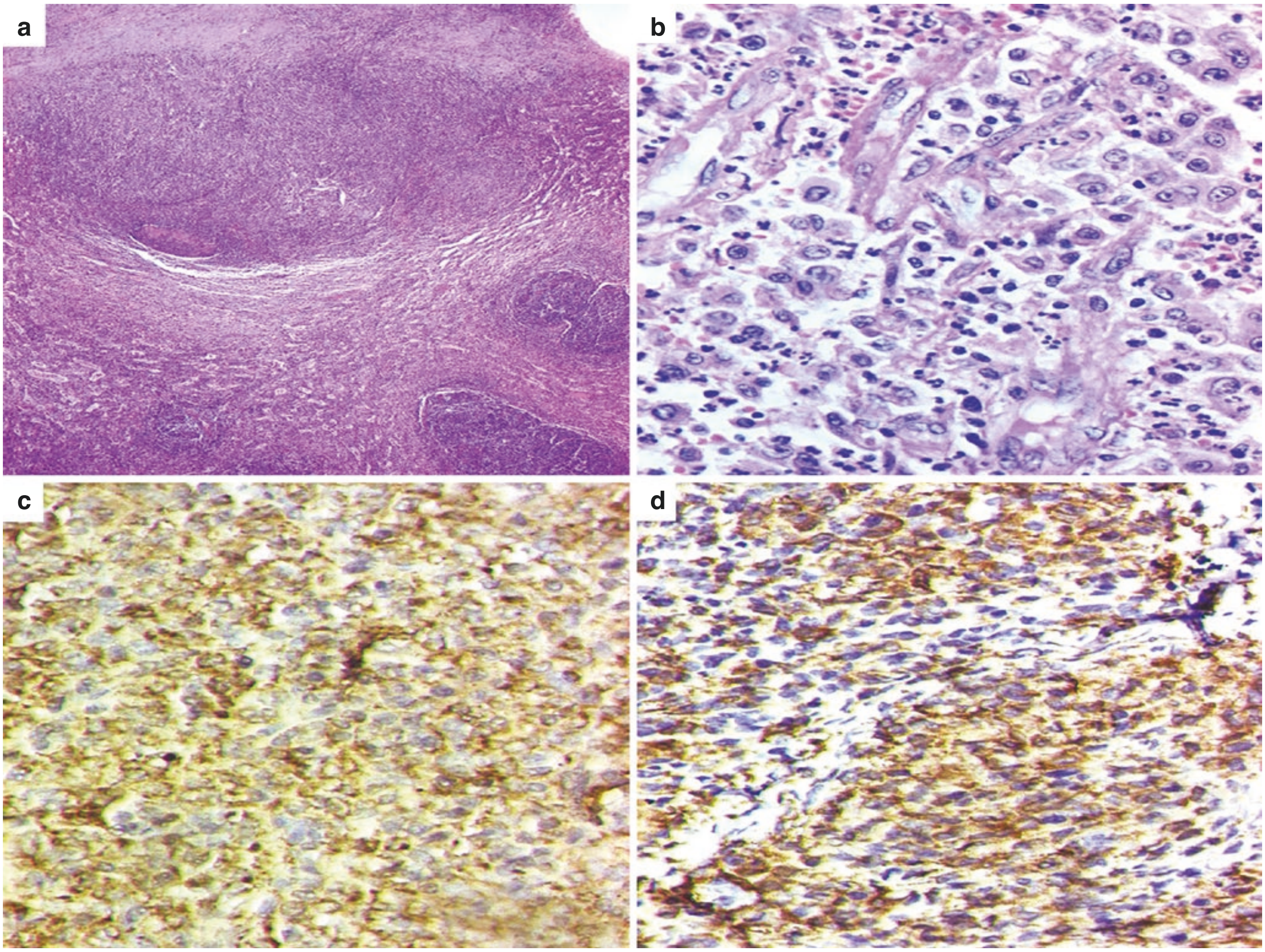

Fig. 1 Representative photomicrographs of splenic histiocytic sarcoma in a 48-year-old male. (**a**) (HE ×40) and (**b**) (HE ×400): Dyscohesive sheets of large cells with abundant eosinophilic cytoplasm with admixed inflammatory cells. The cells show diffuse positivity for CD68 (**c** ×400) and CD163 (**d** ×200)

HSs are aggressive with rare survival beyond 5 years. The localized cased amenable for complete surgical excision however have a better outcome. Currently, no systemic standard treatment recommended, but there are reports of certain degree of responses to *BRAF* and *MAP2K1* inhibitors. Though HS is frequently positive for programmed death ligand 1 (PD-L1) protein, efficacy of anti-PD1 checkpoint therapy is unknown [13].

7 Tumors Derived from Langerhans Cells

Neoplastic proliferation of Langerhans type of cells, which are characterized by immunohistochemical positivity for CD1a, Langerin and S100 protein (see Table 1) and ultrastructural presence of Birbeck granules [10]. These proliferations based on the behavior and degree of aggressive histological features (such as mitotic activity) are classified into Langerhans cell histiocytosis (LCH) and Langerhans cell sarcoma (LCS).

7.1 Langerhans Cell Histiocytosis (LCH)

LCH includes a broad spectrum of clinical manifestations in children and adults, ranging from spontaneously regressive lesions to life-threatening disseminated forms. The diagnosis of LCH is based on clinicoradiological findings along with histomorphological confirmation. It is always advised to do a biopsy for confirmation of suspected LCH lesions.

Historically, LCH was described as three distinct clinical forms: eosinophilic granuloma (≥lytic bone lesions), Hand–Schuller–Christian disease (bone lesions + polyuria + exophthalmos) and Letterer–Siwe disease, a fulminant clinical syndrome (characterized by bone lesions, pancytopenia, hepatosplenomegaly, lymphadenopathy, skin rash, and pancytopenia). The severity of LCH is usually age-related. The current clinical classification of LCH also acknowledges the diverse spectrum, i.e., ranging from localized single-system involvement to disseminated multisystem disease [14]. However, based on the Histiocyte Society working group guidelines, four different groups are defined, depending on the number of organs (or systems) involved, lung involvement and the involvement of one of the three following risk organs (ROs): liver, spleen and bone marrow (i.e., dysfunction of the hematopoietic system) (Table 4) [9].

Table 4 Working group of Histiocyte Society classification of LCH [9]

LCH SS
LCH lung$^+$
LCH MS-RO$^+$
LCH MS-RO$^-$
Associated with another myeloproliferative/myelodysplastic disorder

Abbreviations: *LCH* Langerhans cell histiocytosis, *MS* multiple system, *RO* risk organ (liver, spleen, bone marrow), *SS* single system

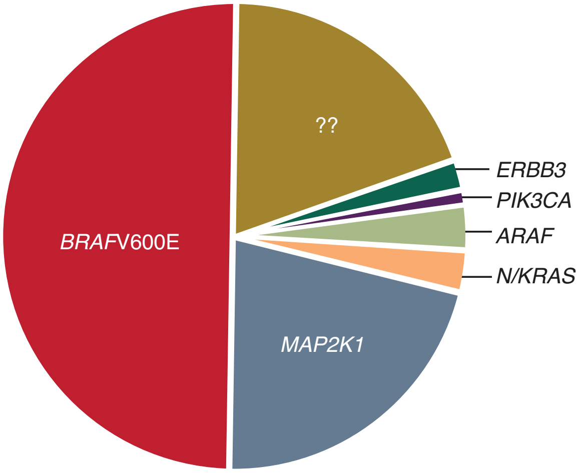

Fig. 2 Pie chart of relative frequencies of activating kinase mutations in LCH (Adapted from [9])

LCH may affect any organ of the body, but bones (80%), skin (33%) and pituitary gland (25%) are the frequent sites in pediatric population. Involvement of liver, spleen, hematopoietic system or lungs is seen in approximately 15%; lymph nodes (5%–10%) and the nonpituitary central nervous system (2%–4%). Lung involvement is more frequent in adults and has been shown an association with smoking. LCH has also been rarely described with other myeloproliferative and T-lymphoblastic neoplasms as phenomenon of transdifferentiation.

Earlier, LCH was considered as dysregulated immune-related disease with abnormal production of cytokines leading to accumulation of LCs with altered cell cycle regulatory mechanisms. However, the identification of clonal alterations, chromosomal instability and telomeric shortening, cell-cycle dysregulation and *BRAFV600E* mutation confirms the neoplastic nature of the disease. Distinct and mutually exclusive activating kinase (ERK) mutations are seen; about 50% of cases show *BRAFV600E* and a fraction of the *BRAF*-wild-type cases show mutations of *MAP2K1, MAP3K1 or ARAF* (Fig. 2). A recent study showed that the mutant allele fraction in LCH was not predictable by tumor cell content and had a significant impact on the efficacy of target therapy. Highly sensitive techniques are therefore recommended in the clinical management of these patients [14–16].

Diagnosis is made from the biopsy from the lesion, which show characteristic histology of atypical large mononuclear cells with coffee bean/kidney-shaped grooved/indented nuclei (sometimes can be lobed) with fine chromatin, inconspicuous nucleoli and thin nuclear membranes admixed with numerous eosinophils, sometimes multinucleated

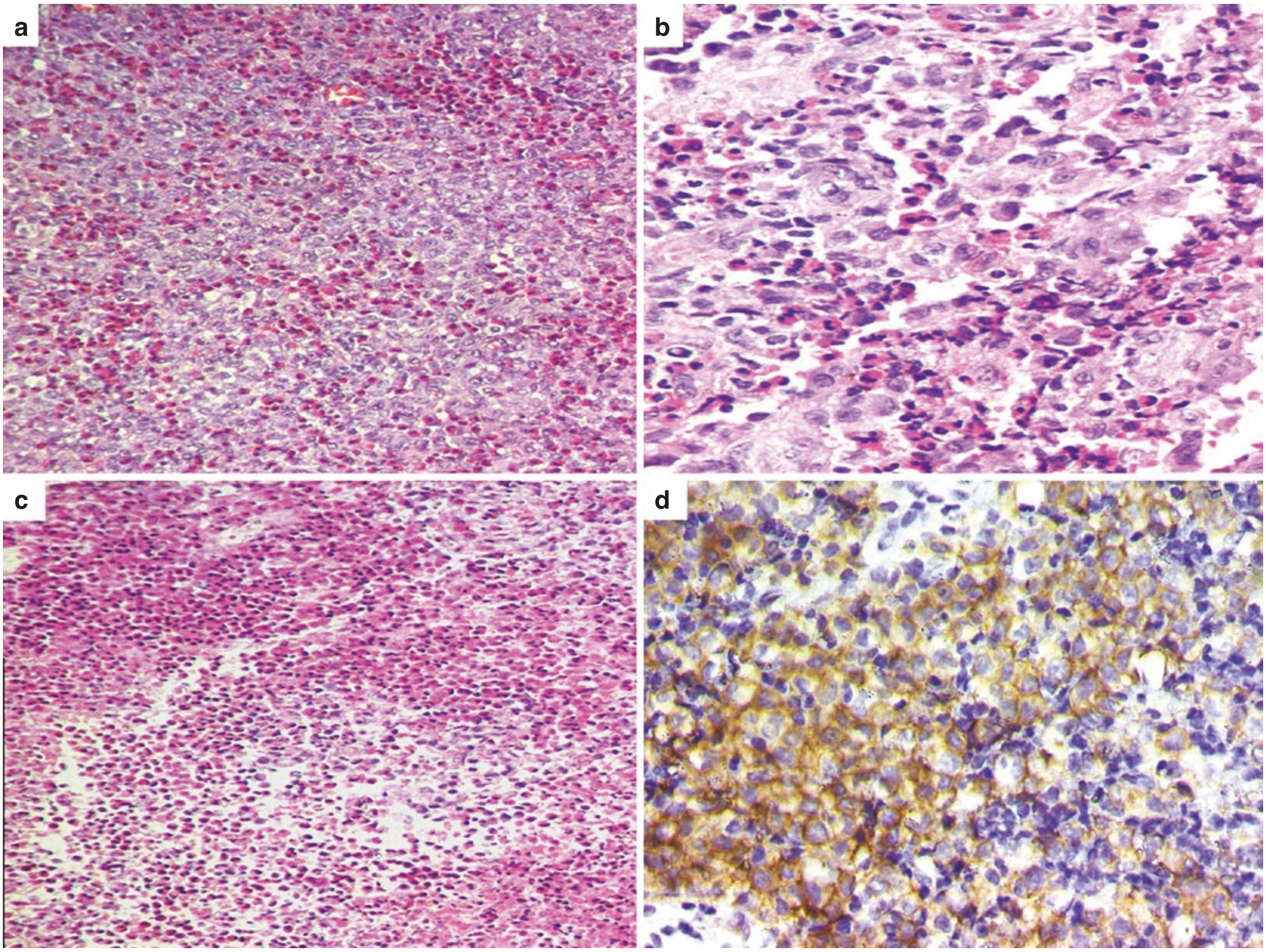

Fig. 3 (**a**) Numerous LCs are seen, with scattered eosinophils. (**b**) Note the typical cytological features of LCs, with many nuclei containing linear grooves. (**c**) Eosinophilic microabscesses. (**d**) The cells show immunopositivity for CD1a

(osteoclast-like) giant cells, neutrophils and small lymphocytes (Fig. 3). Nuclear atypia among the atypical cells is minimal, but mitotic activity is variable and can be high without atypical forms. The cytoplasm is moderately abundant and slightly eosinophilic. Plasma cells are usually sparse. Occasionally, eosinophilic microabscesses with Charcot-Leyden crystals and spotty foci of necrosis can be seen. In early lesions, LCH cells predominate, along with fewer eosinophils and neutrophils. However, with due course of time the percentage of LCH cells decrease; in those instances of late lesions there will be preponderance of foamy macrophages and fibrosis with paucity of LCs. Lymph nodal involvement is usually sinusoidal with secondary infiltration of the parafollicular regions. In spleen, LCH involves the red pulp with nodular pattern sparing the white pulp/periarteriolar lymphoid cell sheath. Liver involvement is usually biliary with sclerosing cholangitis-like pattern. Immunohistochemically, LCH cells are positive for CD1a, Langerin (also called CD207), and S100 protein. In addition, the cells are positive for vimentin, CD68 and HLA-DR. CD45 expression and lysozyme content is low. B-cell and T-cell lineage markers (except for CD4), CD30, and follicular dendritic cell markers are absent. Positivity for PDL1 can also be seen. These features are the same regardless of the extent of the disease.

As a part of standardized clinical work-up, the extent of disease should be assessed in all patients, which can be done by the following tests:

- Complete blood count, serum electrolytes levels and biochemical evaluations, including liver and renal function tests should be done. In cases with hepatomegaly, a coagulation work-up should also be done.
- Urine tests: Routine urinalysis and if indicated (especially to rule out diabetes insipidus), a water-deprivation test also should be done.
- Bone marrow aspirate and biopsy: This should be done in multisystemic cases with anemia and thrombocytopenia.

- Radiologic and imaging evaluation: This is recommended in all cases to categorize as single or multisystemic disease. This should include a whole body skeletal survey and wherever possible with radionuclide scanning especially PET-CT scan.

The clinical course is essentially related to the extent of disease involvement. Extensive multisystemic form is often diagnosed in children ≤5 years with a poor prognosis and mortality rate up to 50%. In infants, even focal disease can sometimes progress to multisystemic involvement. A well-defined unifocal bone restricted disease is primarily a disease of older children and has more than 99% survival probability. Thus, treatment essentially depends on the extent/stage of the disease and is tailored based on the risk stratification [16, 17].

- Low-risk disease (single-system or multisystem):
  - Isolated skin involvement, which has been excised completely, can be observed. In case of residual lesion, can be treated with topical application of steroids with or without psoralen and UV light. However, if no other site is involved, most lesions resolve spontaneously and only observation would be required. Single-site, single lesion disease may not require any intervention.
  - Skull-bone lesions (in the mastoid, temporal, or orbital bones) poses risk for subsequent CNS involvement and thus need to be treated with 6 to 12 months of vinblastine and prednisone. Wherever needed, especially neurological symptoms/defect/instability (in vertebral cases), surgical corrections should be advocated. In cases of vertebral involvement with soft tissue component, chemotherapy is often successful. However, in cases of completely curetted solitary bone lesions, especially in adults may not require any adjuvant therapy.
  - Multifocal involvement (such as multiple bone lesions; or combinations of skin, lymph node, or pituitary gland with or without bone lesions) should be treated with 12 months of vinblastine and prednisone. Bisphosphonates are also effective in extensive bone lesions.
- High-risk multisystemic disease:
  - The standard therapy for high risk organs involvement is combination chemotherapy of vinblastine, prednisone and 6-mercaptopurine for 6 months to 1 year.
  - CNS disease: In case of deficient blood-brain barrier, drugs such as cladribine (2-CdA), or other nucleoside analogs, such as cytarabine, are the best options. In cases with disease-related neurodegenerative features, treatment with drugs like dexamethasone, retinoic acid, intravenous immunoglobulin, infliximab with or without vincristine can be used.

7.2 Langerhans Cell Sarcoma (LCS)

Malignant tumor with overt aggressive histological features and retained immunophenotype of mature LCs [10]. Unlike LCH, LCS is rare and occur in adults, usually affecting skin and soft tissue. Multisystemic forms involving lymph nodes, lung, liver, spleen, and bone are very rare. The clinical features depend on the sites of the involvement and they are similar to LCH. Diagnosis is essentially made on histology, which is characterized by nuclear pleomorphism and a very high mitotic rate (usually >50/10 hpfs). Unlike in LCH, admixture of eosinophils is uncommon in LCS. Immunohistochemical findings are similar to LCH but the expression pattern is more heterogeneous. These patients should be worked up and treated like LCH; however, the prognosis is very bad as compared to LCH [15].

8 Indeterminate Dendritic Cell Tumor

Neoplastic proliferation of cells with immunophenotypic features of normal indeterminate cells, which are thought to be precursors of Langerhans cells (LCs). This tumor is extremely rare and usually presents as multiple/generalized or uncommonly solitary skin nodules, papules or plaques with no systemic symptoms with only rare noncutaneous (lymph node and spleen) presentations [18]. Histologically, the lesions are seen in the dermis with/without involvement of the subcutaneous tissue, composed of histiocytoid cells resembling LCH cells with areas of spindle cell morphology. However, admixed eosinophilic infiltrate is usually not present. Immunohistochemically, the cells are positive for S100 protein and CD1a; while negative for Langerin (CD207), CD163 and dendritic cell markers (CD21, CD23, CD35). Ultrastructurally, they do not show Birbeck granules. *BRAF* and other MAPK-related mutations are rare, while ETV3-NCOA2 gene fusion has been reported in very few cases. Most cases have an indolent clinical evolution, even with spontaneous regression. No prognostic factors are known for these tumors.

9 Interdigitating Dendritic Cell Sarcoma (IDCS)

IDCS are neoplastic proliferation of cells with immunophenotypic features of interdigitating dendritic cells. These are very rare tumors seen in adults usually presenting as isolated enlarged lymph nodal mass with no associated systemic symptoms. Nonnodal, especially skin and soft tissue, involvement has been very rarely reported.

Like the other tumors of this broad group, the diagnosis is essentially histology-based, which shows characteristic paracortical proliferation of ovo-spindloid-shaped cells with fascicular, whorling and storiform architecture. The cells are predominantly mononuclear with variable presence of occasional multinucleated forms. Mitosis is usually low and necrosis is absent. Admixture of small reactive lymphocytes and lesser population of plasma cells are usually seen. Immunohistochemically, the neoplastic cells are positive for S-100 protein, fascin, variably positive for CD68 and CD45. They are negative for CD1a, Langerin, FDC markers (CD23, D21, CD35), CD30, EMA and cytokeratins. Unlike the follicular dendritic cell sarcoma cells, the IDCS cells do not show ultrastructural desmosomes. No specific genetic alterations are reported for this entity. The clinical presentation depends on the site/s of involvement of the diseases. Stage is an important prognostic factor; whereas no clinical correlation was observed for histological features. To date, surgery is the main form of the treatment. They are not shown to be chemosensitive and do not respond to the chemotherapy protocols, especially in cases of nonresectability/incomplete resection, where option of radiation therapy can be considered. The clinical course is usually aggressive with 5-year survival rates of only 50% [11, 19].

10 Follicular Dendritic Cell Sarcoma (FDCS) and Fibroblastic Reticular Cell Tumor (FRCT)

Follicular dendritic cell sarcoma (FDCS) is rare malignant tumor with immunohistochemical phenotype of follicular dendritic cells (FDCs; nonhematopoietic mesenchymal-derived dendritic cells), generally more common in adults. Extranodal presentations are commoner than nodal and are usually not associated with systemic symptoms. About 10% of cases occur in the background of hyaline-vascular type of Castleman disease. Histologically, the neoplastic cells show similar cytomorphological features as that of IDCS but the involvement is usually more diffuse and follicular rather than parafollicular. The tumor can show wide spectrum of histomorphology and thus can mimic different mesenchymal and epithelial neoplasms (Fig. 4). Immunohistochemically, FDCS cells are positive for FDC markers (CD21, CD35, and CD23). Clusterin is often strongly positive (this can serve as good diagnostic differentiating marker from dendritic cell neoplasms as this usually negative or only weakly positive in other dendritic cell tumors). The tumor is variably positive

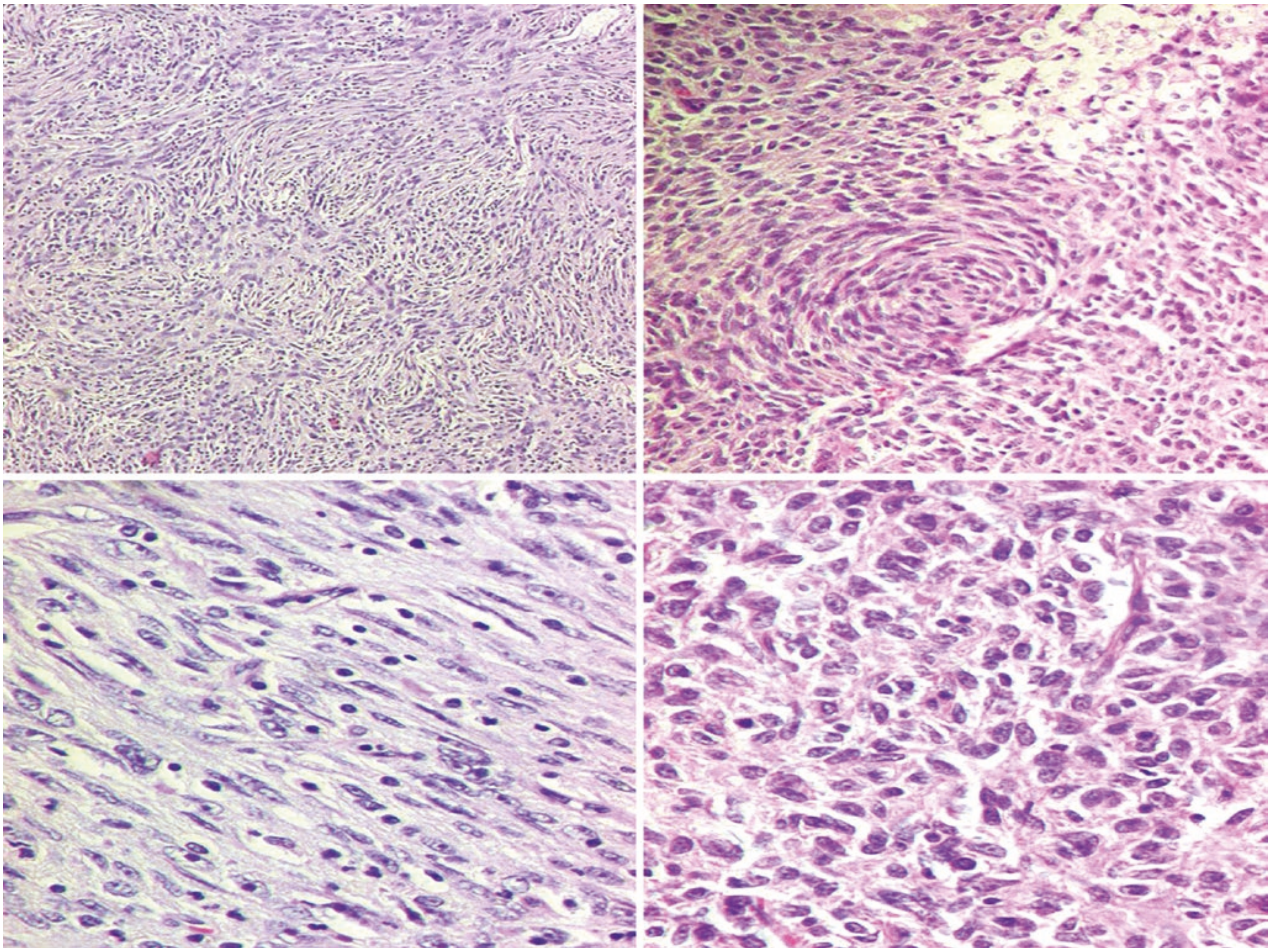

Fig. 4 Follicular dendritic cell sarcoma: histomorphological spectrum

for EMA, S100 protein and CD68; while negative for cytokeratin, Langerin and CD1a. A distinct inflammatory pseudotumor variant (seen predominantly in intra-abdominal locations) shows positivity for EBV. FDCS behavior is variable; the prognosis is excellent in localized surgically excisable cases [20].

FRCTs are also tumors similar to those of IDCS and FDCS but without the immunophenotypic features of IDCS and FDCS. Rather these tumor cells show immunophenotype related to myofibroblast (SMA, desmin and cytokeratin positivity). The clinical and biological basis of these tumor is not much known as they are extremely rare. Thus treatment protocols are similar to that of FDCS and IDCS.

11 Xanthogranulomatous Group of Diseases: Disseminated Juvenile Xanthogranuloma (JXG) and Erdheim Chester Disease

Disseminated juvenile xanthogranuloma (JXG) is characterized by a proliferation of voluminous foamy/xanthomatous histiocytoid cells variably admixed with Touton-type of giant cells with immunophenotypic features of macrophages. They can be solitary or disseminated; the former is more common. Skin and soft tissues are common locations. The disseminated forms usually involve mucosal surfaces of upper aerodigestive tract. No consistent cytogenetic or molecular alterations has been identified. Clinical presentation depends on the sites of involvement—usually related to local mass effect. The CNS forms show LCH-like clinical features; however in liver unlike LCH, JXG do not target biliary system. The clinical course is usually benign (except in CNS, where sometimes the local effects can be catastrophic) but rarely can present with macrophage activation syndromes. Systemic forms that involve liver and bone marrow can been treated like LCH [21].

Erdheim–Chester disease (ECD) is a rare clonal systemic proliferation of cells with similar morphological features of JXG, occurs mostly in adults. It is different from JXG by the presence of the clonal genetic alterations [9]. Majority of patients have multiorgan involvement; commonly involving long bones (>95%), cardiovascular system (50%) and retroperitoneum (30%). Virtually, any organ can be involved in ECD. Osteosclerosis of distal lower limb long bones with pain is a pathognomonic feature. Diagnosis of ECD is essentially based on clinical features, imaging, and histology. Consensus diagnostic criteria for ECD include (1) xanthogranulomatous lesions containing CD68 positive but CD1a-histiocytes, (2) symmetric skeletal uptake of the long bones of the legs on Tc bone scintigraphy, FFDG-PET or MR imaging and (3) involvement of at least one other organ typically affected by the diseases (e.g., xanthelasma, perinephric infiltration, "coated aorta," pericardial infiltration). Molecularly, unlike JXG, ECD shares with LCH of activation ERK signaling pathway in almost all the cases. Almost 95% of cases of ECD show one mutation of the MAPK pathway; BRAFV600E mutation is the commonest (approximately 50%–65%), followed by MAP2K1, ARAF, MAP2K2, NRAS and KRAS. Mutations of PIK3CA have also been reported independent of BRAF status. The clinical course is like a chronic disease and depends on the extent and distribution of the lesions. Though spontaneous regression has been reported, but the disease is usually progressive in untreated patients due to damaging changes on kidneys, the cardiovascular system, lungs and CNS. Like in LCH, CNS involvement is one of the major worse prognostic factors. Treatment with interferon-alpha and targeted BRAF and MEK-inhibitors have been used with good results. However, the duration of the treatment is subject of concern as interruption of treatment has shown to have recurrences [22–24].

12 Rosai–Dorfman Disease/Rosai–Dorfman–Destombes Disease (RDD)/Sinus Histiocytosis with Massive Lymphadenopathy (SHML)

RDD is characterized by proliferation of large, pale histiocytic cells exhibiting emperipolesis, morphologically represented by the intracytoplasmic presence of intact inflammatory cells (usually plasma cells or small lymphocytes). Emperipolesis is an active process of engulfment/penetration of an intact cell into another cell and resides there temporarily without degradation (unlike the process of phagocytosis, which involves degradation and irreversible process). The updated Histiocyte Society classification of histiocytoses categorizes RDD into classical RDD, extranodal RDD, immune-disease-associated RDD, neoplasia-associated RDD and familial RDD (Fig. 5) [9]. Recent molecular studies showed clonal activating kinase mutations involving *KRAS, NRAS, MAPK1* and *ARAF* in a subset, suggesting that RDD represents a neoplastic process at least in some instances. However, unlike in LCH and ECD, *BRAF* mutations are not common in RDD [25].

The classical, i.e., nodal, form usually presents as massive bilateral cervical lymphadenopathy in young individuals. Many (almost up to 40% of cases) show at least one extranodal involvement. Some cases are exclusive extranodal and few can show a systemic involvement. The extranodal sites affected in RDD include nasal cavity and paranasal sinuses, orbital tissue, skin and bones. Central nervous system lesions are very rare are meningeal-based. Patients often present with fever, hyper-gammaglobulinemia, elevated erythrocyte sedimentation and hematological abnormalities. Few cases are shown to be associated with autoimmune diseases like

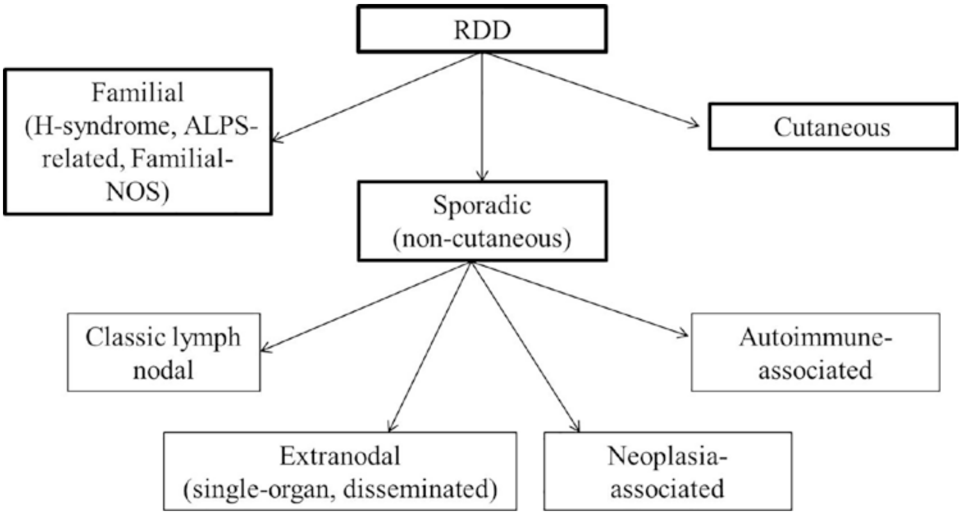

Fig. 5 Schematic classification of RDD as per the updated Histiocyte society working group. *AIHA* autoimmune hemolytic anemia, *ALPS* autoimmune lymphoproliferative syndrome, *ECD* Erdheim–Chester disease, *IJA* idiopathic juvenile arthritis, *LCH* Langerhans cell histiocytosis, *MH* malignant histiocytoses, *NOS* not otherwise specified, *SLE* systemic lupus erythematosus

systemic lupus erythematous, idiopathic juvenile arthritis and autoimmune hemolytic anemia. IgG4+ plasma cells can be elevated, even reaching the cut-off values of IgG4-related diseases; though, the significance of this finding remains unclear, it is now recommended to evaluate for IgG4/IgG ratio is recommended in all RDD cases. The findings of the same should be documented at time of diagnosis [9, 26].

Histologically, the lymph nodes characteristically show dilated sinuses filled by large pale macrophages containing intracytoplasmic variable numbers of undamaged lymphocytes, neutrophils and plasma cells (emperipolesis) (Fig. 6). The rest of the nodal parenchyma shows prominent plasma cell infiltrate. Immunohistochemically, the macrophages are typically positive for S100, CD68 and CD163; while negative for CD1a and Langerin (CD207). Plasma cells are usually polyclonal with a variable fraction of IgG4+ cells. Extranodal RDD shows a relative more heterogeneous morphology of small foci or scattered typical macrophages admixed with dense polymorphic inflammatory infiltrate and fibrosis. The macrophages can be obscured by the inflammatory cell infiltrate and moreover, emperipolesis can be negligible. In these cases, S100 immunopositivity with clinical correlation can be very helpful to identify. The familial cases also show similar histomorphological features as described for sporadic lymph nodal and extranodal cases.

Sporadic RDD has a good outcome; asymptomatic patients with adenopathy and cutaneous disease can be observed. Surgical excision may be indicated in unifocal extranodal disease or for mass-related symptomatic cases. Those with multifocal irresectable extranodal disease may require systemic therapy. Though there is currently no standardized regimen; different systemic therapies for these patients include corticosteroids, sirolimus, chemotherapy, immunomodulatory and radiotherapies. In cases with severe and refractory diseases, targeted next generation sequencing for mitogen-activated protein kinase (MAPK) mutations is advised for institution of potential targeted therapy if any variant identified.

Key Points

- Histiocytic and dendritic cells tumors are rare, and diagnosis is histology-based and requires an appropriate panel of immunohistochemical markers and in some instances, molecular tests and clinical features.
- Histiocytic sarcoma should be considered in all tumors showing large atypical cells with abundant eosinophilic cytoplasm lacking markers of more common high-grade lymphoid and nonlymphoid neoplasms in absence of monocytic leukemias.
- Diagnosis of Langerhans cell histiocytosis is substantially based on the typical histology of coffee bean-shaped grooved nucleated histiocytoid cells admixed with eosinophil-rich inflammatory cells infiltrate and osteoclast-like giant with a typical immunohistochemical expression of CD1a, Langerin/CD207 and S100. Detection of *BRAFV600E* mutation is useful to support diagnosis in doubtful cases. Treatment strategy is stage-based.
- Indeterminate dendritic cell histiocytosis/tumor differs from Langerhans cell histiocytosis by lack of Langerin/CD207 expression.
- Erdheim–Chester disease diagnosis is now separated from Juvenile xanthogranulomas by the presence of genetic alterations (*BRAF, MAP2K1, ARAF, MAP2K2, NRAS and KRAS*); though it may share the clinical, radiological and pathological features.
- Rosai–Dorfman/Rosai–Dorfman–Destombes disease represents a heterogeneous group of disorders all characterized by tissue infiltration by S100 protein positive large macrophages exhibiting emperipolesis. At least a subset of them are clonal, thus neoplastic.

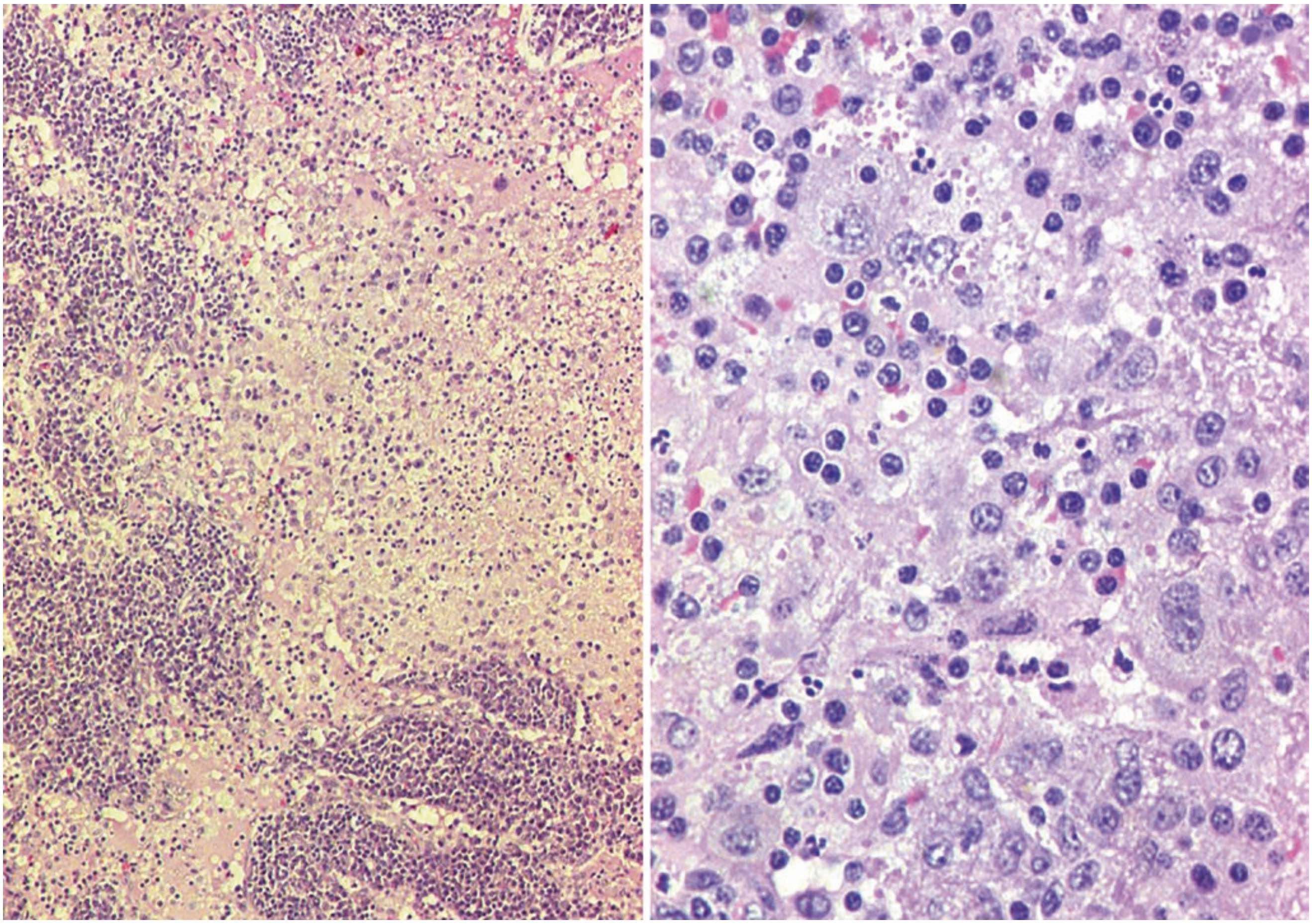

Fig. 6 Nodal Rosai–Dorfman disease, characterized by large pale macrophages with emperipolesis of other inflammatory cells

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Pediatric Acute Leukemias

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Abbreviations

AAR	Age-adjusted rate ATRA all-trans retinoic acid
ALL	Acute lymphoblastic leukemia
Allo-SCT	Allogenic stem cell transplant
AMKL	Acute megakaryoblastic leukemia
APML	Acute promyelocytic leukemia
ATRA	All-trans retinoic acid
B-ALL	B-lineage ALL
CAR	Chimeric antigen receptor
DIC	Disseminated intravascular coagulation
HiDAC	High-dose cytarabine
HLA	Human leucocyte antigen
ICiCLe	Indian Childhood Collaborative ALL Protocol
InPOG	Indian Pediatric Oncology Group
LSC	Leukemic stem cell
MDRO	Multi-drug resistant organism
MLL	Mixed-lineage leukemia
MRD	Minimal residual disease
MSD	Matched sibling donor
Mtx	Methotrexate
MUD	Matched unrelated donor
NCI	National Cancer Institute
PBCR	Population-based cancer registry
POD	PML oncogenic domains
RXR	Retinoic-X receptor
SNIP	Single nucleotide polymorphism
TLS	Tumor lysis syndrome
WGS	Whole genome sequencing

1 Introduction

The term leukemia ("white blood" from Greek leukos [white] and haima [blood]) was coined by Rudolph Virchow in 1845 for a blood disease with a splenic enlargement [1]. By 1913, four types of leukemia were recognized—chronic lymphocytic and myelogenous leukemias, acute lymphocytic leukemia, and erythroleukemia. Childhood leukemia was, however, not differentiated into lymphoid or myeloid till 1950, and was invariably fatal due to bleeding and/or infection [2]. It is now broadly classified into acute lymphoblastic, myeloid, and mixed phenotypic leukemias—ALL, AML, and MPAL, respectively. Within the AMLs, Acute Promyelocytic leukemia (APML) is considered sufficiently distinct to merit separate attention. For the purpose of this chapter, ALL, AML, and APML are discussed as separate entities.

2 Acute Lymphoblastic Leukemia

2.1 Introduction

The modern therapy for childhood leukemia began with Sidney Farber, a Boston-based pathologist, who first used 4-amino pteroylglutamic acid (aminopterin) an analog of methotrexate (synthesized by Y. Subbarow, a New York-based pharmacologist) to treat 16 children with acute undifferentiated leukemia [3]. Temporary remissions with clinical, hematological, and pathological improvements were recorded in ten children, ushering in the modern age of cancer chemotherapy [4]. During the 1950s and 1960s, new drugs were discovered including the vinca alkaloids, anthracyclines, 6-mercaptopurine (6-MP), and platinum compounds, leading to the first combination chemotherapy trials by Frei and Freireich at the National Cancer Institute (NCI), Pinkel and Holland at Roswell Park Cancer Institute and Burchenal at Memorial Sloan-Kettering Cancer Center [2].

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The current 5-year survival rates in childhood ALL have crossed the 90% mark, thanks to the excellently designed clinical trials conducted by various groups around the world, aided by the rapid progression of technology including genetic techniques, flowcytometry and pharmacogenomics [5], as well as vast improvements in supportive care. Unfortunately, even today 90% of children with ALL in the world's poorest 25 countries die in sharp contrast to the high-income countries where 90% of children get cured of the disease [2].

2.2 Incidence and Epidemiology in India and Global

ALL remains the most common malignancy of childhood, representing nearly one-third of all childhood cancers and 75% of all cases of childhood leukemia. The annual incidence is about 34 per million children in the United States [6], up to 40 per million among industrialized Western European, and 30–35 cases per million in Eastern European countries [7]. The incidence is lower in sub-Saharan Africa (20 per million). In India, a recent study compiling statistics from 24 population-based cancer registries (PBCRs) that clubbed India into six regions—North, South, East, West, Central, and Northeast, showed age-adjusted rates (AAR) of leukemia ranging from 0 (in some districts) to 62.3 per million (pm) for girls and 0 to 101.4 pm for boys in the age-group 0 to 14 years for the years 2012–2014, with most cases occurring in the North, South, and West regions of the country. However, these may not be fully representative, though they still give us the most specific data to date [8]. A rough projection from this data would give us a figure exceeding 10,000 new cases per year, which if accurate is higher than the population incidence seen in most developed countries. The peak age of ALL is 2–5 years and is more common in boys, the difference being greatest among pubertal children. White children are more commonly affected compared to blacks in the US.

2.3 Clinical Presentation in India and Global

ALL and its clinical presentation are best understood in the context of its etiology and interplay of genetic and environmental factors. While these are complex and largely obscure, many factors including genetic, immunological infections, and environmental factors are now considered causative. A prenatal origin of ALL was supported by finding TEL-AML1 (or ETV-RUNX1) fusion gene in some leukemic blasts in neonatal dry blood spot samples (Guthrie cards). This was however also found in 1% of all neonatal samples tested, a frequency 100 times higher than the incidence of ALL in children, suggesting a second hit mutation for leukemogenesis [9, 10]. The commonly encountered mixed-lineage leukemia (MLL) rearrangements occur in 80% of cases of infants with ALL and may be prenatal in origin [11]. ALL may also occur in identical twins, a risk which gradually decreases with age suggesting in-utero events like metastasis of leukemic clones—probably due to twin-to-twin metastasis, synchronous genetic events, or simultaneous prenatal exposure to environmental leukemogens [12]. Familial clustering of cases of ALL also lends support to the genetic origin of childhood ALL. Less than 5% of all childhood ALLs are associated with inherited genetic syndromes. Children with trisomy-21 are 15–20 times more likely to develop leukemia when compared to normal children [13]. Other less common syndromes predisposing to acute leukemias include Klinefelter's, Beckewith-Weideman syndromes, and germline BRCA2 mutations. Children with neurofibromatosis, Schwachman's syndrome are also reported to increase the risk of ALL. Syndromes leading to defective repair of chromosomes (Fanconi's anemia and Bloom's syndrome) have also been found to increase the risk [14].

Prenatal radiation exposure and higher birth weight have also been consistently associated with an increased risk of childhood ALL. Higher maternal age and history of fetal loss, parental smoking, and alcohol use, exposure to pesticides or solvents, and exposure to high levels of residential high power-frequency magnetic fields have all been proposed to enhance the risk of childhood ALL whereas perinatal maternal vitamin supplementation and population folate fortification have been associated with reduced risk. Infections have also been attributed to leukemogenesis; wherein delayed exposure to common infections (Greaves hypothesis) and population mixing (Kinlen's hypothesis) can potentially give rise to leukemia [15, 16].

The classification of ALL has also evolved over time from a simple morphological-based one, to a complex one incorporating immunocytochemistry, flow cytometry, and genetic and molecular characteristics. After several attempts to classify ALL by morphological criteria, the French-American-British (FAB) Cooperative Working Group came out with a classification system of ALL into ALL-L1, ALL-L2, and ALL-L3 [17]. Approximately 85% of children have ALL-L1, 14% have ALL-L2 and the rest 1% have ALL-L3. Representative morphology is depicted in Fig. 1. However, morphology does not correlate well with immunophenotype, cytogenetics, or DNA-microarray-based classification system [18]. In the current era with a wide range of risk predictors for the outcome of ALL at hand, the value of morphological classification in the treatment of these patients is fast losing its relevance [19].

With the advent of monoclonal antibodies, improvement in the enzymatic and fluorescent tagging of these antibodies, and the development of multi-parameter FACS, ALL has been classified immunophenotypically into two broad

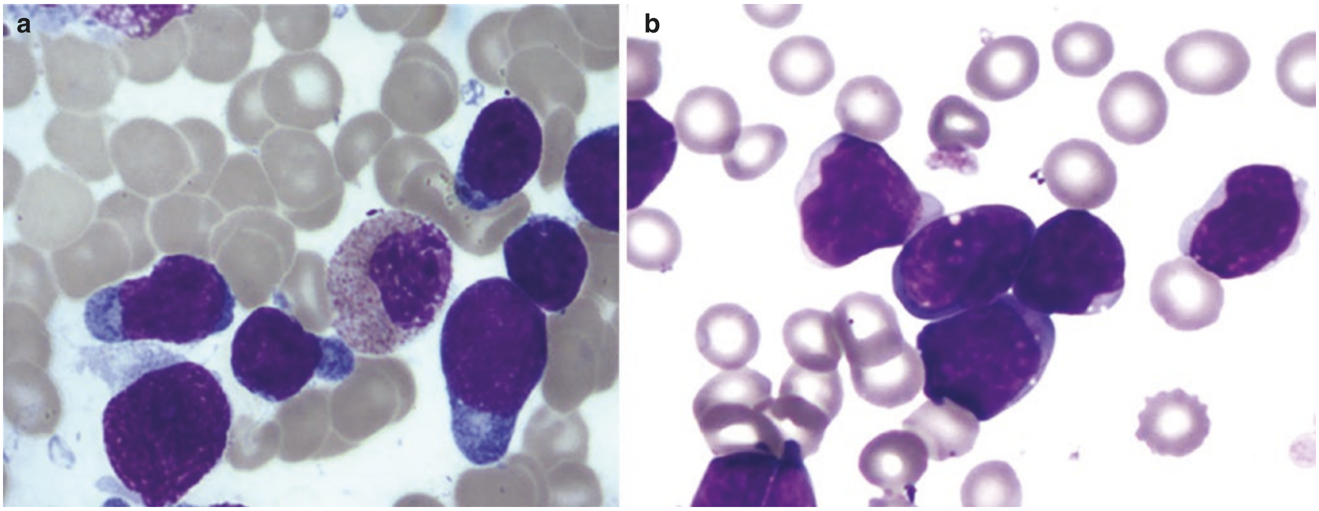

Fig. 1 Photomicrographs of blast morphology in ALL. (**a**) Precursor T lymphoblastic lymphoma/leukemia. (**b**) Precursor B lineage ALL. (Images courtesy of Dr. Nikhil Patkar, Hematopathology Laboratory, Department of Hematopathology, TMH, Mumbai)

classes: (1) B-cell ALL and (2) T-cell ALL, which in turn are further classified into several subgroups based on differences in immunophenotypic markers [19]. These subtypes of ALL have distinct genetic signatures which help to characterize these subgroups better and are of prognostic importance. Conventional cytogenetics, RT-PCR, fluorescence in-situ hybridization, and flow cytometry are increasingly used to detect specific fusion transcripts, gain or loss of cellular DNA content, or specific chromosomes with prognostic or therapeutic relevance [20]. Recent studies, including one by our group, have shown that an integrated genomic profile that includes copy number alterations may be prognostic in B-lineage ALL (B-ALL) [21].

However, from the therapeutic point of view, it is essential to classify ALL into three varieties—namely, precursor B-ALL, mature B-ALL, and T-cell ALL [20].

2.4 Precursor B-ALL

Traditionally, about 70–80% of B-ALL cases were classified by modal chromosomal number (ploidy) and specific genetic rearrangements into prognostically relevant subgroups. Now, with the advent of genome-wide analyses, virtually all B-ALL cases can be classified genetically. Hyperdiploidy (>50 chromosomes/blast cell) is associated with a good therapeutic response as these cells are more prone to apoptosis and accumulate more methotrexate polyglutamate. Hypodiploidy (fewer than 45 chromosomes per leukemia cell), found in less than 2% of cases, confers a poor outcome. Many translocations have been found to be of prognostic significance. TEL-AML1 (ETV-RUNX1 fusion) fusion the commonest translocation in precursor B-ALL portends favourable prognosis. MLL-AF4 arising due to t(4;11) is known to be a poor prognostic factor in childhood ALL, whereas MLL-AF4 due to t(4;11), MLL-ENL due to t(11;19) and MLL-AF9 due to t(9;11) are also associated with poor prognosis. Translocation t(9;22) fuses the BCR gene on chromosome 22 to the ABL gene on chromosome nine causing an abnormal ABL tyrosine kinase activity associated with increased proliferation and decreased apoptosis, this translocation is mainly found in B-ALL. Its incidence increases with age from 3% in children to nearly 25% in adults with ALL. It is considered high-risk due to resistance to standard chemotherapy and high postinduction MRD. However, the advent of targeted therapy using tyrosine kinase inhibitors (TKI) has improved outcomes to 75–80% 3-year EFS [22]. Recently, intra chromosomal amplification of chromosome21 (iAMP21) identified in about 2% of cases of precursor B-ALL, more in adolescents, has been identified as a high-risk disease responding poorly to standard therapy.

Using high-throughput techniques like single nucleotide polymorphism (SNIP) arrays and whole genome sequencing (WGS), deletions, amplifications, insertions, and other structural rearrangements were identified in patients with poorer outcomes with otherwise normal cytogenetic risk factors. Blasts with these mutations including IKZ1 mutations, PDGFR beta, ABL1, and ABL2 translocations were found to express genetic signatures similar to Ph+ve ALL and patients harboring these mutations benefit from TKI inhibitors [23].

2.5 T-Cell ALL

T-ALL being a biologically heterogeneous disorder compared to B-ALL has been less well characterized genetically. However, high throughput assays have identified new genetic signatures for T-ALL, though their clinical significance are being identified. More than 50% of cases of T-cell acute lymphoblastic leukemia have activating mutations that involve *NOTCH1*, a gene encoding a transmembrane receptor that regulates normal T-cell development. The presence of NOTCH1 mutation seems to predict a favorable outcome for T-cell ALL [24]. Epigenetic silencing of cyclin-dependent kinase inhibitor 2A (CDKN2A) gene leads to the inactivation of tumor suppressor genes leading to the neutralization of the TP53 and the retinoblastoma pathways in nearly 70% of the T-ALL cases. This mutation appears to confer a poor prognosis.

2.6 Special Types of ALL

2.6.1 Infant ALL

ALL of infancy appears to be biologically unique, arising from a very early stage of commitment to B-cell lineage and having unique genetic signatures as compared to older children. They express HLA-DR, but are usually negative for CD10 and other mature B-cell markers, instead of myeloid markers viz. CD15 may be positive. Structural abnormalities in chromosome 11 particularly rearrangements in band 11q23/MLL are frequently seen. The presence of MLL-AF4 rearrangement portends a poor prognosis despite intensified chemotherapy and HSCT [25]. Clinical trials specifically recruiting infant ALLs are looking into ways to improve the outcome including the use of novel agents for this poor prognosis disease.

2.6.2 Philadelphia-Chromosome Positive ALL

The presence of BCR-ABL translocation historically resulted in poor outcomes. Matched-related transplantation was recommended for all children with this subtype of ALL, and survival outcomes in the pretyrosine kinase-inhibitor era were 35 ± 4% (3-year EFS) with chemotherapy, and 57 ± 22% and 72 ± 19% with matched-related transplantation and matched-unrelated transplantation respectively [26]. The use of imatinib in combination with an intensive chemotherapy backbone improved results greatly to a 3-year EFS of 80 ± 11% [22]. The availability of second-generation TKIs has made it easier to treat Imatinib-resistant cases and Dasatinib is currently under trial for the treatment of pediatric ALL.

2.6.3 Adolescent ALL

Older adolescents 15–21 years of age have an inferior outcome as compared with that of children and younger adolescents with ALL, partly due to an increased incidence of Philadelphia chromosome-positive and T-cell ALL, lower incidence of *ETV6-RUNX1* fusion or hyperdiploidy, and poorer compliance [27, 28]. They also suffer more toxicities. However, it is also established that adolescents and young adults do consistently better when pediatric treatment protocols are used [29].

The presenting signs and symptoms in a child with ALL reflect the impact of bone marrow infiltration with the abnormal leukemic cells and the extent of extra-medullary involvement. Pallor (88%), fatigue, bone pain (23%), petechiae-purpura (48%), and fever (60%) are common symptoms at presentation. Lymphadenopathy (50%) and hepatosplenomegaly (68%) are frequent manifestations of extra-medullary leukemic involvement. T-cell ALL, seen in 15% of cases may present with a distinct set of sign-symptoms including an older child, commonly male with a very high total leukocyte count at diagnosis and commonly have a mediastinal mass [30]. A high proportion of children (10–15%) presenting with T-ALL may have CNS involvement at presentation.

Rarely children with ALL may present with signs and symptoms of unusual extra-medullary organ (ocular, urinary bladder, and pancreas) involvement. Hypereosinophilia with its attendant clinical features (Loeffler’s syndrome) is another well-documented but relatively rare feature at presentation, seen in association with translocation t(5;14). An elevated total leukocyte count of >10,000/mm^3 is seen in nearly 50% of the patients, with half of them having counts of more than 50,000/mm^3. Anemia (hemoglobin <10 g%) is seen in nearly 80%. Thrombocytopenia is seen in most patients, with nearly 75% of patients having a platelet count of <1,00,000/mm^3 [14].

2.7 Evaluation and Work-Up Including Risk Stratification

To establish a diagnosis of ALL a bone-marrow examination is necessary. Documentation of more than 25% lymphoblasts in the bone marrow by morphology and cytochemical staining (ALL− PAS±, Tdt+; AML− Peroxidase+, Sudan Black+) establishes ALL. Immuno-phenotyping by flow cytometry and genetic analyses further define and also stratify childhood ALL. Baseline organ function including liver function, renal function, cardiac function (echocardiography), and chest radiograph also need to be done pretreatment.

A variety of other laboratory abnormalities may be associated with childhood ALL. Many of these findings and their degree of severity merely reflect the leukemic cell burden, the extent of extra-medullary spread, or the excess proliferation and destruction (turnover) of the neoplastic cells. The rapid turnover of leukemic cells may lead to the classical “tumor lysis syndrome” (TLS) manifested by hyperuricemia, hypocalcemia, hyperphosphatemia, hyperkalemia, and deranged renal function. Children with high tumor burden (high initial leukocyte count, large lymphadenopathy, and hepatosplenomegaly) are predisposed to TLS, and it may precede or occur after initiation of therapy. Hepatic dysfunction may occur due to infiltration by leukemic cells and may not correlate with hepatomegaly. Patients may present with mild renal function derangements initially due to renal infiltration without any bearing on the disease outcome. Coagulation abnormalities may occur infrequently at diagnosis and disseminated intravascular coagulation (DIC) is rare [14].

2.8 Principles of Management (an Integrated Brief Overview of Rx Philosophy)

Treatment of ALL involves a remission-induction phase, followed by intensification/consolidation, interim-maintenance phase, and re-induction/delayed intensification followed by continuation/maintenance phase (Fig. 2).

2.8.1 Remission Induction Phase

The goal of this phase is to eradicate 99% of the initial leukemic burden, restore normal hematopoiesis, and improve the functional status of the patient [28]. The primary target is the medullary disease load. Combinations of glucocorticoids (prednisolone or dexamethasone), along with at least two other drugs (vincristine and L-asparaginase or an anthracycline) [31] are used. A three-drug induction is usually sufficient for most of the standard risk diseases, provided they receive an adequate postremission treatment. Children with high-risk or very high-risk ALL receive an induction comprising four or more drugs. The induction phase aims to induce complete morphologic remission, and preferably MRD remission, in 4–6 weeks.

The treatment response is monitored during induction by various means: (1) Response to initial steroid prephase by peripheral blast count, (2) By bone marrow blast count at predefined time points between 1–3 weeks and 4–5 weeks of the start of induction, (3) By assessment of minimal residual disease (MRD) at various time points during induction like day 14 and/or day 35. A post-steroid day 7 peripheral blast count of >1000/mm^3, M2 or M3 marrow status (>5% and >25% bone-marrow blasts) or MRD >1% at day 14 are predictive of poor response and calls for a high-intensity post-induction therapy. In fact, response during induction (most importantly, MRD at day 35) is one of the single most important predictors for the overall outcome of ALL [13].

2.8.2 Intensification/Consolidation Phase

The aim is to eradicate minimal residual leukemia and drug-resistant leukemia from the system and the sanctuary sites (CNS, testes, etc.). Intensification is essential for all patients, but again there is no consensus on the best regimen or duration of treatment. Consolidation treatment is generally given soon after remission induction and includes drugs that were not included in induction (e.g., cyclophosphamide, cytarabine) [31].

2.8.3 Interim Maintenance

This is a phase of treatment following intensification and preceding re-induction, which varies according to the risk

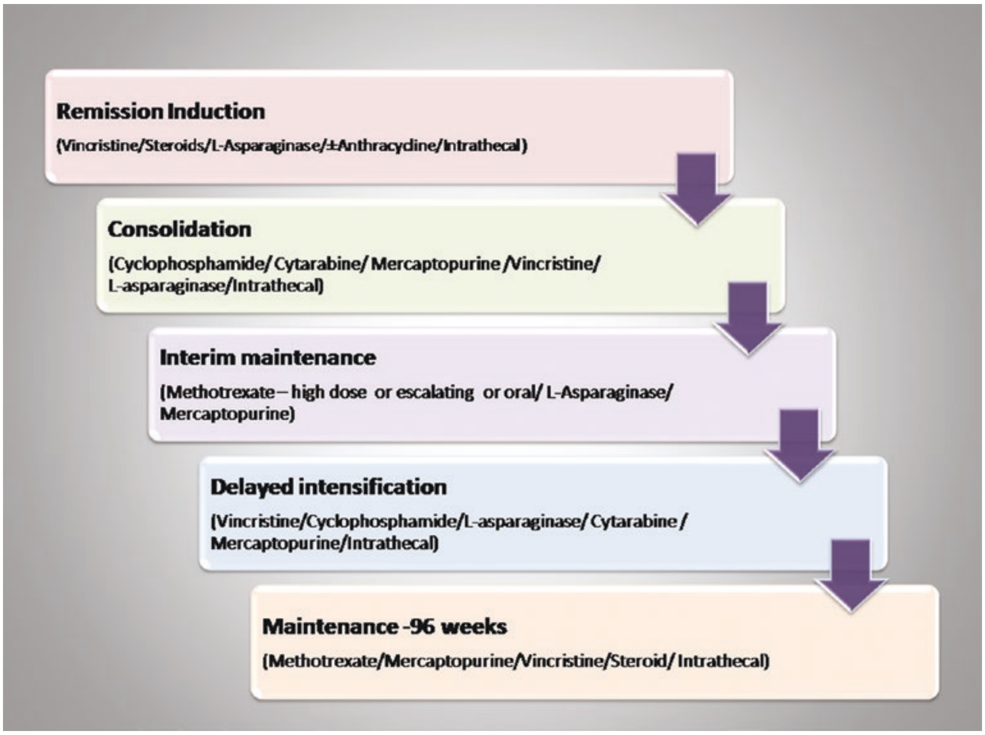
Remission Induction
(Vincristine/Steroids/L-Asparaginase/±Anthracycline/Intrathecal)
Consolidation
(Cyclophosphamide/ Cytarabine/ Mercaptopurine /Vincristine/ L-asparaginase/Intrathecal)
Interim maintenance
(Methotrexate – high dose or escalating or oral/ L-Asparaginase/ Mercaptopurine)
Delayed intensification
(Vincristine/Cyclophosphamide/L-asparaginase/ Cytarabine / Mercaptopurine/Intrathecal)
Maintenance -96 weeks
(Methotrexate/Mercaptopurine/Vincristine/Steroid/ Intrathecal)

Fig. 2 Schematic presentation of phases of treatment (including commonly used drugs in each phase)

group of ALL and includes high-dose methotrexate with leucovorin and mercaptopurine (in case intensification comprised of non-HD-Mtx regimen) or escalating doses of methotrexate with pulses of L-asparaginase in high-risk B-ALLs [31, 32].

2.8.4 Re-induction/Delayed Intensification Phase

Delayed intensification, given within 2–3 months after remission, is clearly beneficial to all patients. The main purpose of this phase is to prevent disease relapse. More than one course of delayed intensification has not shown any additional benefit in outcomes but adds to the toxicity [33].

2.8.5 Continuation/Maintenance Phase

A prolonged maintenance therapy for 2 years is given for ALL, or even longer in some protocols. The aim is to prevent late relapses. Maintenance consists of daily 6-mercaptopurine (6-MP) and weekly methotrexate (Mtx). In some protocols, additional pulsed glucocorticoid, vincristine, and intrathecal therapy are administered. During continuation treatment with weekly low-dose methotrexate and daily mercaptopurine, tailoring the dosages of these drugs to the limits of tolerance has been associated with a better outcome [34].

2.8.6 Central Nervous System (CNS) Directed Therapy

CNS is the most important sanctuary site for leukemic cells and the commonest site of extra-medullary relapse of ALL, accounting for 30–40% of initial relapses. The penetration of systemic chemotherapy into the CNS is erratic, necessitating CNS-directed therapy. These include (1) the use of appropriate systemic chemotherapeutic agents in adequate doses, (2) intra-thecal therapy, and (3) judicious CNS radiation.

Intensified systemic therapy like dexamethasone, high-dose methotrexate, L-asparaginase, and 6-thioguanine used during various phases of treatment along with intrathecal therapy abrogates the need for prophylactic CNS radiation. Prophylactic radiation usually is given in a dose of 12 Gy. The need for CNS radiation (CRT) is currently limited to patients with overt CNS leukemia (CNS-3) only, in a dose of 18 Gy, many co-operative groups have stopped using cranial RT even in CNS-3 patients [35].

2.9 Medical Management and Monitoring

Patients should be stabilized and worked up rapidly on arrival (Table 1). Stabilization encompasses the prevention and treatment of tumor lysis syndrome, transfusion of blood products, and treatment of any co-existent infection. Patients presenting with compression of mediastinal/vital structures might need urgent initiation of cytotoxic drugs [14]. Patients need close monitoring for tumor lysis during the initial days of induction. Chances of infection during induction are high and need aggressive management, necessitating close follow-up and a good emergency response system. Postinduction follow-up is mostly guided by treatment protocol and the patient's clinical condition.

Response assessment is protocol based. However, the most important one is bone-marrow MRD at day 35 of induction (<0.01%—MRD remission/negative) [13]. Patients failing to clear MRD post-induction continue on high-risk protocol and undergo repeat assessment at the end of consolidation. Patients with persistent MRD positivity postconsolidation should be offered intensive chemotherapy followed by an allogeneic stem cell transplant.

The value of repeated bone-marrow MRD assessments once remission is achieved is questionable and is not recommended. It may be used to assess remission in a pre-SCT recipient [36]. Post therapy-completion, patients are followed-up clinically and with routine blood tests 3 monthly for the first year, then 6 monthly for 2 years, and annually thereafter.

2.10 Management Algorithms According to Risk Stratification

Risk-stratification of ALL is a comprehensive process involving the clubbing of clinical, pathological, and genetic factors, to which early response to therapy has also been added. Most contemporary protocols follow a similar strategy. There have been no new drugs in the treatment of ALL in the last three to four decades, though some drugs have newer, more effective formulations. Protocols have evolved around the world using the same few drugs in various combinations and schedules, more by trial and error. These have now been refined, along with great strides in supportive care measures, and evolved into strategies that are universally accepted. The first risk-stratification evolved from a workshop sponsored by the National Cancer Institute (NCI) in 1993, which involved all the major centers, and groups treating Pediatric ALL in the United States [37], now popularly called "NCI risk-groups". Different groups follow slightly different stratifications based on local strategies and needs. We present the one followed at our institute, a comprehensive amalgamation of the NCI risk criteria and current concepts (Table 2) [38].

2.11 Prognosis with Current Rx

Pediatric ALL has been one of the highly curable malignancies for several years now, with strides in each decade as outcomes improved from below 10% in the 1960s to above

Table 1 Diagnostic and initial management algorithm of PHL DMG at TMH

Assess if patient needs admission. Discussion with consultant.

Outpatient	**Inpatient** **(Discuss plan with consultant)**
Hr 0: - Assess need for transfusion	- IV fluids at 3L/m^2 (D5NS with I/2 NS if Na>138)
- Allopurinol (xyloric) (10 mg/kg/day)	- If in TLS, consider rasburicase (see TLS management) - L- Asparaginase if hyperleukocytosis ± Hydroxyurea in AML
- Syrup digene	-Maintain hemoglobin more than 7 gm% & platelets > 20,000/cmm.
- Plenty of oral fluids	- Antibiotics if fever ▪ Start chemotherapy once stable ▪ social worker review ▪ Nutritionist Review

Day 1:
- F/U daily or more frequently (as needed) with CBC, RFT, Ca, Mg, Phos, Uric acid
- Nutritional counseling
- To meet social worker

Day 2:
- Collect bone marrow reports
- Counsel the family /take consent
- To meet counseling nurse in OPD
- Diagnostic spinal tap with first IT on Day 2-8 based onprotocol (Mtx on Day 8 in ALL and TIT on day 2 in AML)
- Send CSF for cytospin, cell count, cytomorphology and biochemistry
- Start induction therapy (usually after admission)

Day8:
- Collect cytogenetics, CSF reports and blast cell count on PS

Day35:
- Bone marrow studies with MRD assessment

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90% in developed countries [39, 40]. Recently, with the increased use of more aggressive "pediatric-like" protocols in adolescents and young adults (AYAs), their prognosis too has improved somewhat [29, 41]. In India, the outcomes of Pediatric-ALL hovers around 60–70% in most centers. The challenges are the poor socio-economic status of the majority of our country with resultant issues like limited access to quality care, travel to referral centers and uprooting of families, malnutrition, limited availability of blood products, disruption of job, income, and education, and related problems that result in high rates of treatment abandonment, and also poor tolerance to toxic chemotherapy. A recent global survey identified many of these factors [42]. However, creating robust and comprehensive socio-economic support systems from government and non-government agencies can have a profound effect on decreasing treatment abandonment and

Table 2 Risk stratification of pediatric ALL and AML

Risk group	ALL	AML
Standard/ good risk	Age: 1–9 years Non-T-cell Prednisolone good response No high-risk cytogenetics WBC ≤50,000/mm^3	Inv(16) or t(16:16) t(8:21) t(15:17) Normal cytogenetics with Bi CEBPA or NPM mutation
Intermediate risk	Good risk But age ≥10 years or WBC ≥50,000/mm^3 Bulky disease Testicular disease	Normal cytogenetics +8 t(9:11) Other nondefined
High risk	All T-cell immunophenotype Prednisolone's poor response on D8 CNS disease on day 8 High-risk cytogenetics – MLL rearranged – Hypodiploidy (<45 chromosomes) – t(9:22), iamp21 – t(17:19) – MRD positive postinduction (>0.01%)	Complex (≥3 clonal) karyotype −5, 5q−, −7, 7q− 11q 23 [Non(9:11)] Inv(3) or t(3:3) t(6:9) t(9:22) Flt 3-ITD allelic ratio >0.4

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reducing mortality [43]. We showed that more than 250 patients of pediatric ALL who started treatment with us in 2010 had an overall survival (OS) of 67%, and treatment abandonment declined from above 30% in 2010 to consistently below 5% since 2013. In 2013, we also adopted the risk-stratified and treatment-response-based protocol of the Indian Pediatric Oncology Group (InPOG) [44], named Indian Childhood Collaborative ALL Protocol (ICiCLe), and piloted it from March 2013 to February 2018. An interim analysis of 726 children showed projected 3-year OS was 90.4 ± 1.4% (median follow-up—23 months), while EFS was 70.7 ± 2.3%. Seventy percent of mortality occurred in intensive phases of treatment, and 86% of all events in non-SR arms. Three-year OS for standard-risk patients exceeded 95% [45].

2.12 Management of Recurrent Disease Including Specific Palliative Measures

Despite excellent results of contemporary pediatric ALL protocols, 15–20% of pediatric ALL and nearly 30–45% of adolescent and young adult ALL cases relapse [41, 46]. Being one of the most commonest malignancies in children, the relapse burden is commensurately high, making ALL-relapse the fourth most common pediatric malignancy [47]. With the increasing use of MRD evaluation, end-induction levels above 0.01% predict EFS of 30–59%, while those who are negative (<0.01%) have more than 88% EFS [48]. Treatment decisions are now based on MRD assessed by FCM or molecular techniques [36, 48]. Current protocols allow for a risk-adapted approach and treatment escalation in those who are MRD-positive at the end of induction. These patients are reassessed after consolidation. MRD-positive at this time are considered chemotherapy-refractory requiring alternate strategies.

Treatment of relapse/refractory ALL is difficult as it involves intensive chemotherapy ideally followed by an allogeneic stem cell transplant (Allo-SCT) in patients with high-risk features at relapse. Allo-SCT however, is capital and human-resource-intensive, and most crucially requires a matched donor, preferably a sibling (matched sibling donor, MSD), with the same human leucocyte antigen (HLA) signature in at least 10 loci. Being somatically inherited, the chances of two siblings being HLA matched is less than 25% depending on family size and ethnic/familial cloistering [49]. Matched unrelated donor (MUD) SCTs are several folds more expensive [50]. Most donor registries are in developed nations and of differing ethnicities resulting in lower chances of matching in Indian patients [51]. Moreover, the timing of the relapse with respect to disease-free interval affects the chances of a successful Allo-SCT. Early medullary relapses defined as occurring within 36 months of first remission (CR1) have only 20–40% successful outcomes, while extramedullary relapses or those beyond 36 months of first remission may have 60–70% outcomes [46]. Patients need to be in remission again (CR2) with MRD-negative status prior to SCT [52]. This involves intensive chemotherapy to achieve and sustain CR2 till such Allo-SCT. As number of centers doing Allo-SCTs are still few when compared to the need, this often proves challenging and extremely toxic for the patients. Allo-SCT itself carries significant morbidity and TRM, and many patients may suffer long-term complications especially GVHD and infections related to long-term immunosuppression, which tend to increase over time [53]. Unlike developed nations, in India, the expenses and technical difficulties involved result in less than 10% of patients who might benefit from an SCT opting for one, and only a fraction making it through the entire process. Allo-SCT, being an extensive topic in itself, is outside the purview of this chapter.

Developments in genetic engineering, biotechnology, and immunotherapy have brought forth many ALL-specific therapies including monoclonal antibodies and engineered cellular immunity against cell surface markers of leukemic blasts. They are mostly in early-phase human studies and some are now licensed and in phase-3 clinical trials. These include anti-CD19 antibodies (Blinatumomab), anti-CD22 antibodies (Inotuzumab and Epratuzumab), and CD19/CD22 or CD19 and CD22 bispecific Chimeric Antigen Receptor (CAR) T-cells, which have shown promising efficacy in managing relapsed/refractory disease [54].

3 Acute Myeloid Leukemia

3.1 Introduction

Myeloid is derived from the Greek word 'Muelos' meaning bone marrow. Cells belonging to the granulocytic (neutrophilic, eosinophilic, basophilic), monocytic/macrophage, erythroid, megakaryocytic, and mast cell lineages comprise the Myeloid series. Therefore, malignancies of the myeloid series are a heterogeneous group of disorders, caused by genetic aberrations in hematopoietic stem cells with unlimited self-renewal capacity with a certain degree of myeloid differentiation. These genetic aberrations are divided into Class I and Class II mutations. Class I mutations confer a proliferative and anti-apoptotic advantage, while class II mutations cause inhibition of normal hematopoietic cell differentiation [55]. The leukemic stem cell (LSC) is difficult to eliminate, and a major cause of relapse [56, 57]. Intensification of therapy to eliminate the LSC increases the risk of toxic deaths during and after treatment. Prolongation of chemotherapy has not helped either [58]. The UK-MRC trials showed five courses of chemotherapy were not superior to four [59]. Allogeneic HSCT in CR1 for high-risk diseases with the aim to exploit the graft-versus-leukemia effect is being used as a strategy to improve relapse-free survival [58, 60].

Myeloid leukemias are acute in more than 95% of children. Juvenile myelomonocytic leukemia is exclusive to the pediatric age group and has poor outcomes worldwide, with transplantation in CR1 offering some benefits [61, 62]. About 10% of children with Downs' syndrome have transient abnormal myelopoiesis (TAM), and 20% of them develop acute megakaryoblastic leukemia (AMKL), which often has good outcomes with lower doses of chemotherapy because of higher sensitivity to them [63]. Myelodysplastic syndrome is rare in children, but AML associated with underlying bone-marrow failure syndromes is a different topic beyond the scope of this chapter.

3.2 Incidence and Epidemiology in India and Global

In children, ALL is five times more common than AML. About 10,000 new cases of pediatric AML are registered worldwide [64]. In our 5-year experience, we have seen about 2262 cases of ALL and 517 cases of AML with a ratio of 4.3:1, which mirrors the global experience. A comprehensive review of acute leukemias from 24 PBCRs in India, gave data on acute leukemias (refer to section of ALL), but did not segregate AML [8].

3.3 Clinical Presentation in India and Global

These patients often present with hyperleukocytosis, and with infections due to prolonged neutropenia and severe malnutrition. In general, the presentation of AML can vary, but in India, most are present with advanced-stage disease. Pallor and fatigue, petechiae and mucosal bleeds, and recurrent fevers mostly bacterial and fungal, are common. Bone pain is not uncommon and patients might present with a limp or rib pain or back pain. The extramedullary disease may present with (1) hepatosplenomegaly more frequent in infants, (2) leukemia cutis with blueberry muffin appearance in infants with monocytic differentiation, or (3) granulocytic sarcoma of the orbit and epidural area mostly in AML M4 and M5. Involvement of the testes is rare. In one series, about 20% of patients had myeloid sarcoma frequently associated with t(8;21), and had a better outcome even in the absence of t(8;21) [65]. CNS involvement at diagnosis occurs in 15% of patients.

3.4 Evaluation and Work-Up Including Risk Stratification

A peripheral smear can raise suspicion for acute leukemia and is a critical investigation, especially for acute promyelocytic leukemia. A detailed evaluation with bone-marrow aspiration and biopsy is essential. Myeloperoxidase stains are positive in the blasts. Morphology of a bone-marrow biopsy can identify features of myelodysplasia, or underlying fibrosis as in the case of AMKL. Immune phenotyping at diagnosis is valuable to confirm the FAB phenotype and is more useful for MRD monitoring to assess response to treatment. Chromosome karyotyping and molecular cytogenetics help in risk stratification, prognostication, and identification of associated genetic predispositions. Currently, WHO classification uses specific and recurrent cytogenetic abnormalities to stratify AML as:

- AML with recurrent genetic abnormalities
- AML with myelodysplasia-like features
- Therapy-related AML
- AML not otherwise specified
- Myeloid sarcoma
- Myeloid proliferation related to Down syndrome

Table 3 Classification of AML with characteristics

AML FAB type	Chromosomal abnormality	Affected genes	Characteristics
M0			Less common in pediatrics
M1, M2	t(8;21)(q22;q22)	RUNX1-RUNX1T1	MPO+, Auer rods, granulocytic sarcoma, no HSCT if t(8;21)+ Standard risk
M3 M3v	t(15;17)(q22;q12) t(11;17)(q23;q12)	PML-RARα PLZF-RARα FLT3 aberrations	Coagulopathy, ATRA sensitive, favorable prognosis, no HSCT ATRA resistant, poor prognosis Hyperleukocytosis, ATRA sensitive, favorable prognosis
M4eo	inv(16)(p13;q22) t(16;16)	MYH11-CBFβ	CNS leukemia; eosinophilia with basophilic granules favorable prognosis, no HSCT Standard risk
M4, M5a M5b	t(11q23) anomalies t(8;16)	MLL rearrangements MYST3-CREBBP	Infants or young adults, hyperleukocytosis, erythrophagocytosis and coagulopathy, granulocytic sarcoma, and secondary leukemia after topoisomerase II inhibitors t(4;11) are specially associated with infants presenting with CNS and skin involvement
M6		Chromosome 5&7	Less common in paediatrics, >50% blasts are erythroblasts, Flow + glycophorin A
M7	t(1;22) Trisomy 21	RBM15-MKL1	AML in infants with Down syndrome, myelofibrosis, favorable prognosis, CD41+, CD61+ Non-Downs AMLM7 without t(1;22) have a poor prognosis
M2, M4, MDS	t(6;9) inv(3) t(3;3)(q21;q26)	DEK-NUP214 EVI1	Basophilia Prior to MDS, thrombocytosis and abnormal platelets
MDS	−7/del(7)(q22-q36) −5/del(5)(q11-q35) +8		Exposure to toxins, MDS progressing to AML, less common in children

Many clinicians still find it easy to correlate FAB classification with clinical features. Table 3 [66] shows the correlation between different AML FAB subtypes and underlying chromosomal aberrations and associated clinical characteristics.

3.5 Principles of Management (an Integrated Brief Overview of Rx Philosophy)

Chemotherapy for AML consists of two cycles of chemotherapy for remission-induction, followed by postremission therapy which includes two cycles of consolidation for standard-risk patients and HSCT for high-risk patients. CNS prophylaxis with triple intrathecal chemotherapy keeps CNS relapse rate <5%. Most cooperative group trials use aggressive induction with 3+7 induction regimen with anthracycline for 3, and cytarabine for 7 days, with or without etoposide or thioguanine [58, 59]. This is followed by postremission therapy with high-dose cytarabine (HiDAC)-based regimens. Newer agents to achieve better remission induction while minimizing anthracycline-related cardiotoxicity are incorporated in the different phases of treatment [67].

3.6 Risk Stratification

Patients with recurrent genetic abnormalities t(8;21) and inv [16] and double mutant CEBPA are considered standard/low risk [68]. Patients with complex cytogenetics, MDS/monosomy or del 5 and 7, FLT3-ITD are considered high-risk patients and are eligible for transplant in CR1. Patients who do not qualify for either, are classified as intermediate-risk. These patients are managed based on the MRD status at the end of the first and second cycles of chemotherapy. The St Jude group uses MRD <1% after the first induction cycle and <0.1% at the end of induction as the cutoff for decreased risk of relapse [58]. The risk-stratification strategy at TMH is given in Table 2.

3.7 Treatment at TMH

At TMH we often see patients who present late. High white counts at presentation are common, with a risk of TLS. Cytarabine and hydroxyurea have been used to reduce the leukemia burden before definitive chemotherapy. We have seen good results with L-asparginase in rapidly reducing the leukemia burden without TLS. We use a standard 3+7 Induction for all AMLs. A bone-marrow morphology is done on day-10. If any blasts are present, the patient gets additional Ara-C 8 g/m^2 (four divided doses 12 hourly × 4) on day-10 and 11. Bone-marrow studies are repeated on count recovery in either case. Frank induction failures are shifted to a salvage regimen with the Cladarabine-Cytarabine combination. The rest are continued on high-dose cytarabine (HiDAC) blocks. MRD assessment is done post-induction and if positive, repeated at the end of the first consolidation regimen. Patients MRD-negative by the end of the first or second cycle of chemotherapy get a total of three HiDAC blocks. They then get one-year maintenance of oral metronomic chemotherapy (OMCT) with 6-thioguanine (40 mg/m^2) and oral Etoposide (50 mg/m^2) 3 weeks followed by a 1-week break making one cycle [69, 70]. Patients not achieving MRD-negative status by the end of the second cycle of intensive therapy, are changed to the salvage regimen as above. All patients needing a salvage regimen are counseled for Allo-SCT. Patients who are MRD-positive after two cycles of salvage regimen are considered palliative. All high-risk patients are also counseled for SCT in the first remission. In patients with very poor general condition at presentation due to severe malnutrition, invasive fungal infections, or multi-drug resistant organism (MDRO), we use the OMCT strategy upfront, allowing them to stabilize, while reducing the disease burden and creating an opportunity to withstand subsequent standard intensive therapy. OMCT is also used to palliate patients failing to achieve remission as it allows them to go home with a reasonable quality of life till the inevitable progression.

We have also investigated the use of disease-modifying agents in AML. Sorafenib is an oral biaryl-urea derivative that can inhibit the Ras/Raf/MAP/ERK signaling pathway. It also inhibits tyrosine kinases like VEGFR, c-kit, PDGFR-β, and FLT-3. Due to its potent Tyrosine-kinase inhibitory activity, especially, its ability to inhibit FLT-3 kinase, we use it in combination with chemotherapy for patients with FLT3 mutations (FLT3-ITD). A very important aspect for improvement in outcomes would be supportive care, which can have a deep impact on disease-free survival in AML, and other pediatric cancers [43].

3.8 Relapsed AML

Once relapsed or refractory, AML is difficult to treat. Remission induction with Cladarabine Ara C has been somewhat successful in our hands but the remission is short-lived unless patients undergo Allo-SCT.

3.9 Future Directions

Immune-based therapies are being explored to improve outcomes for AML since we have hit a ceiling with the amount of chemotherapy that can be given. Some groups are using gemtuzumab ozogamicin to target the C33-positive leukemic stem cells. At St. Jude, haploidentical KIR mismatched NK cells are being used as consolidation therapy to prolong remission [60]. Still, others are exploring the use of chimeric antigen T cells directed against sCD123 and CD33 that might be able to get rid of the leukemic stem cells to achieve sustained remission.

4 Acute Promyelocytic Leukemia

4.1 Introduction

Acute promyelocytic leukemia (APML/AML-M3) is characterized by (a) typical morphology of blasts, (b) t(15;17), and (c) specific coagulopathy [71]. A sound understanding of the biology of APML has changed it from having the worst to the best prognosis among AML subtypes.

The reciprocal translocation t(15;17) of retinoic acid receptor-α (RARα) locus on chromosome-17 and the PML locus on chromosome-15 results in the PML-RAR-α fusion protein, which is a dominant negative inhibitor of promyelocytic leukemia protein and retinoic-X receptor (RXR) present in macromolecular nuclear organelles called PML oncogenic domains (POD), and disrupts their localization. All-trans retinoic acid (ATRA) binds to the RARα domain leading to re-localization of the PML and RXR proteins rescuing the cell from differentiation arrest. Arsenic, on the other hand, binds to the PML domain causing degradation of the fusion protein an effect similar to ATRA. In addition, Arsenic causes degradation of the wild-type PML protein leading to apoptosis of the cell. The non-cross-resistant mechanism of action of these two agents has led to improved outcomes in APML [72].

4.2 Incidence

APML accounts for about 10–15% of patients with AML. Data in the Indian setting is lacking. At TMH 15% of AML patients had APML.

4.3 Principles of Management

Treatment of APML has evolved in three phases. Pre-ARTA era, ATRA + chemotherapy era, and ATRA + Arsenic era. In the pre-ATRA era high-dose anthracyclines were used in combination with cytarabine with CR rates of 65–80% of which 50% relapsed. Early death due to coagulopathy or chemotherapy resistance was a major cause of mortality [71].

The introduction of ATRA upfront allowed better control of coagulopathy. The combination of ATRA and chemotherapy resulted in 80–90% CR rates and could result in long-term relapse-free survival of about 70% [73]. Later, the focus shifted to reducing anthracycline-induced cardiomyopathy and improvement of quality of life. LoCoco in 1993 showed that a combination of ATRA + Arsenic might even be superior to ATRA + chemotherapy. In the Arsenic + ATRA era, Sanz risk stratification and maintenance gradually lost their significance. All patients received the induction and consolidation with ATRA + arsenic. Patients with high tumor burden received chemotherapy or biological agents like Gemtuzumab ozogamicin [74]. In the MRC AML17 trial, ATRA + Arsenic had very good CR rates and a cumulative incidence of relapse of 1% [75]. In all these trials, pediatric patients were enrolled and analyzed separately on the same protocol. In the ATRA trials, pediatric patients had a higher incidence of pseudotumor cerebri and the dose of ATRA was reduced to 25 mg/m^2 with no difference in efficacy [75, 76].

A patient presenting with characteristic coagulopathy and increased promyelocytes on a peripheral smear should be immediately started on Arsenic or ATRA as per the local protocol. It is justified to stop it later if the suspicion proves to be incorrect. Morphologically two different variants exist, the classic, and M3v microgranular variants. The latter is associated with FLT3 mutation or ITD and hyperleukocytosis [77]. A quick FISH test to look for t(15;17) is useful but RT-PCR is the gold standard for diagnosis and response assessment. Five percent of APML patients present with atypical breakpoints with alternative chromosomal alterations, and might not be sensitive to ATRA. However, arsenic and ATRA have non-cross-resistant pathways and their combination might help in these cases.

4.4 Management and Monitoring

Patients with APML are at high risk of DIC. Monitoring of blood counts and PT/PTT/INR at 6–8 hourly intervals is essential. Transfusion of platelets to keep count above 30,000/μL and fibrinogen above 1.5 g/L using FFP or cryoprecipitate helps prevent catastrophic bleeding. ATRA causes differentiation of promyelocytes and reduces the risk of coagulopathy but predisposes to differentiation syndrome. Chemotherapy, on the other hand, causes tumor lysis and leads to coagulopathy. Therefore, a combination of ATRA and chemotherapy is used to achieve a fine balance. Children are at a high risk of pseudotumor cerebri and a lower dose of ATRA at 25 mg/m^2 is used. Arsenic can cause hepatotoxicity and prolonged QTc interval predisposing to arrhythmias. Monitoring electrolytes, especially potassium, calcium, and magnesium are helpful to prevent arrhythmia. In case of hepatotoxicity, prolonged QTc, differentiation syndrome, or pseudotumor cerebri, withholding treatment for a few days manages the side effect appropriately and it can then be restarted at a lower dose [74–76, 78].

4.5 Treatment Algorithm

4.5.1 Induction

Arsenic 0.15 mg/kg daily + ATRA 25–45 mg/m^2 is given in two divided doses until complete hematological remission or day-60. Anthracycline can be given in case of hyperleukocytosis or added if WBC count rises to >6000 at day-5, >10,000 at day-10, or >15,000 on day-15 since they are at higher risk of differentiation syndrome [71].

4.5.2 Consolidation

Arsenic is given for 4 weeks on 4 weeks off for 4 cycles. ATRA is given 2 weeks on and 2 weeks off for 7 cycles.

4.6 Common Toxicities

Differentiation syndrome is seen after introducing ATRA or arsenic, and the patient presents with respiratory distress, sudden weight gain, pleural and pericardial effusion, hypotension, and cardiac or renal failure. Dexamethasone at 5 mg/m^2/dose twice a day and stopping ATRA and arsenic until resolution of differentiation syndrome and restarting at 50% of the dose with escalation over 2–3 days is an effective treatment.

About 10% of children mostly below 10 years of age present with headache blurry vision nausea and vomiting. Computerized tomography (CT) scans of the head show no evidence of bleed. This has led it to be called "pseudotumor cerebri." ATRA and arsenic should be stopped until the resolution of symptoms and acetazolamide can be started at 8 mg/kg up to 250 mg three times a day [78].

Arsenic can cause prolonged QT interval. Electrolytes and ECG are monitored on a weekly basis and withheld if QTc is more than 0.45 s.

4.7 Management of Recurrent Disease

Patients who relapse of non-arsenic protocols are given arsenic as a single agent and autologous transplant can be considered in CR2. For patients who have received arsenic previously arsenic + ATRA can be given in combination with Bortezomib with a 3-year EFS of 92% [79].

5 How We Do It at TMC

From the mid-1980s till 2013, we treated all patients of ALL on the MCP841 protocol, first introduced in India as a medium-intensity protocol meant for out-patient delivery and did not incorporate high-dose methotrexate. Initial results on it improved outcomes to above 50% and reduced relapse rates compared to those treated with a less intensive protocol [80]. Later, outcomes improved to 67% [43]. However, the protocol underwent several modifications from its original form in this period. Since March 2013, we have adopted the ICiCLe protocol as a pilot, initially only for B-ALLs. As shown earlier, this may be able to result in 5-year OS in the range of 75–80%, as 3-year results have been encouraging [45]. However, the impact of improved supportive care strategies including socio-economic support, aggressive nutrition intervention, uninterrupted availability of blood products, an effective social worker team to track and retain patients, and even continued schooling, in improving outcomes, cannot be ignored [43]. Effective March 2018, we are offering all our patients with B-cell ALL, T-cell ALL, and lymphoblastic lymphomas to participate in the trial. We are still using the previous multicentre protocol (MCP 841) to treat children with Mixed phenotype acute leukemias (MPALs) as it contains consolidation with high-dose cytarabine that has proved useful in this poor prognosis risk group [81]. To address the issue of relapsed/refractory B-ALL we are in the process of developing indigenous CAR T-cell therapy in collaboration with the Indian Institute of Technology-B (IIT-B) in Mumbai, which may prove effective at affordable costs.

For acute leukemias, we have formulated a diagnostic and initial management algorithm that can be common to all of them until they are started on individual protocols as already discussed (see Table 1).

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Pediatric Hodgkin Lymphoma

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Abbreviations

ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine
ABVE-PC	Doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide
AV-PC	Doxorubicin, vincristine, prednisone, cyclophosphamide
AYA	Adolescent and young adult
BOOP	Bronchiolitis obliterans organizing pneumonia
CBC	Complete blood counts
cHL	Classical Hodgkin lymphoma
COPDac	Cyclophosphamide, vincristine, prednisolone, dacarbazine
COPP/ABV	Cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine
DBVE	Doxorubicin, bleomycin, vincristine, etoposide
DECA	Dexamethasone, etoposide, cisplatin, cytarabine
eBEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine
EBV	Epstein–Barr virus
ESR	Erythrocyte sedimentation rate
HL	Hodgkin lymphoma
IFRT	Involved field radiotherapy
ISRT	Involved site radiotherapy
LDH	Lactate dehydrogenase
LFT	Liver function tests
NLPHL	Nodular lymphocyte predominant Hodgkin lymphoma
OEPA	Vincristine, etoposide, prednisolone, doxorubicin
PET-CT	Positron emission tomography-computerized tomography
RER	Rapid early responder
SER	Slow early responder
SPPD	Sum of the product of perpendicular diameters
SST	Secondary solid tumors
USG	Ultrasonography
VAMP	Vinblastine, doxorubicin, methotrexate, prednisone

1 Introduction

Hodgkin lymphoma (HL) is one of the pediatric malignancies with excellent survival [1]. It is fair to say that in the race to cure malignancies, HL was among the first to wear the "curable cancer" tag. Initial treatment regimens in children were similar to those used for adults, but the differential impact of long-term morbidities seen especially in children and young adults including secondary malignancies, permanent gonadal toxicity leading to infertility, and cardiotoxicity led to successive risk-based, gender-based, and response-based trials in children. From combined-modality treatment

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involving chemotherapy and radiotherapy to all, these trials have helped tailor treatment by reducing chemotherapy in lower-risk groups and avoiding radiotherapy in those children with good responses. Newer trials are ongoing, incorporating targeted agents in frontline therapy. Significant progress has also been achieved in the relapsed and refractory setting with improved survival.

2 Incidence and Epidemiology in India and Global

HL accounts for 5–6% of pediatric malignancies [2] with an annual incidence of about 0.5 cases per 100,000 children in the United States and European Union [3]. In India, lymphomas often exceed CNS tumors in children as opposed to the developed world, with Hodgkin lymphoma exceeding non-Hodgkin lymphoma, which seems to result mainly from the higher incidence of HL in male children <14 years of age [4].

Epidemiologically, there are three distinct forms of HL: a childhood form (≤14 years), an adolescent and young adult (AYA) form (15–34 years), and an older adult form (55–74 years). In the developed world, the early peak occurs during the middle-to-late 20s compared to the developing world where it is seen before adolescence [5]. Reports from various resource-limited countries show that there is an increased incidence of HL before five years compared to the industrialized countries [6]. There is slight overall male preponderance in the childhood form, while gender distribution is almost equal among the AYA group.

In Western countries, 75% of newly diagnosed patients have early disease at presentation (stage I–II) while more than half of the patients in the developing world have advanced disease (stage III–IV). The most common histologic subtype is mixed cellularity probably related to early Epstein–Barr viral (EBV) exposure compared to the developed world where nodular sclerosis dominates in the AYA population [4]. The risk of HL is also increased among individuals with primary immunodeficiencies, HIV infection and those on post-transplant immunosuppression [7–11].

3 Clinical Presentation in India and Global

Most patients present with painless lymphadenopathy (80%), commonly involving the cervical or supraclavicular area. These lymph nodes are firm, rubbery, non-tender, and tend to be matted. There is typically contiguous spread along adjacent lymph node regions as opposed to non-Hodgkin's lymphoma. The mediastinal disease is seen in 75% of the AYA population compared to 35% in younger children reflecting the different histological sub-types in these age groups. Primary sub-diaphragmatic disease is rare and is seen in <3%. Fever (oral temperature >38 °C), weight loss (≥10% body weight within preceding six months), and drenching night sweats are constitutional symptoms that have prognostic significance [10].

Laboratory findings are nonspecific and include anemia mostly due to failure of iron store mobilization, elevated erythrocyte sedimentation rate (ESR), neutrophilic leukocytosis, lymphopenia, eosinophilia, thrombocytosis, and monocytosis.

Paraneoplastic syndromes are rarely associated with HL such as nephrotic syndrome, autoimmune hemolytic anemia, neutropenia, thrombocytopenia (ITP), polymyositis, idiopathic cholestasis, and limbic encephalitis [11]. Autoimmune hemolytic anemia may be Coombs positive and may be diagnosed before, at the time of disease diagnosis, or after therapy. ITP may develop after treatment completion and does not predict relapse. Its treatment and response are similar to non-HL-related ITP.

4 Evaluation and Work-Up Including Risk Stratification

4.1 Diagnosis

An excision biopsy of the suspected lymph node is preferred as it helps evaluation of Hodgkin's and Reed Sternberg (HRS) cells and the architectural changes seen in the different subtypes. In case of inaccessible sites where excision biopsy is not possible like retro-peritoneum or mediastinum, a core needle biopsy can be performed. HRS cells form only 0.1–10% of the tumor tissue, the bulk of which is inflammatory cells, therefore fine needle aspiration (FNAC) does not provide sufficient diagnostic tissue material and should be avoided. The diagnosis is established by histology and immunohistochemistry (IHC). HL is a B-lineage lymphoma arising from germinal center B cells characterized by clonal tumor cells in a polymorphous inflammatory background comprising T-lymphocytes, eosinophils, plasma cells, neutrophils, histiocytes, and fibroblasts [12].

HL can be classified into two main pathologic classes [12].

- Classical HL (cHL)
- Nodular lymphocyte predominant HL (NLPHL)

cHL is further subdivided into four types as below

- Nodular sclerosis
- Mixed cellularity
- Lymphocyte rich
- Lymphocyte depleted

4.2 Immunohistochemistry

HRS cells express CD30, with 70% of patients with CD15 positivity and 10–20% with CD20 positivity. Generally, they are negative for CD45, B-lineage antigens (CD19, CD79a, OCT2, BOB1) and bcl-6 [13]. Approximately 98% have dim PAX-5 expression and they often express plasma cell molecules (CD138, MUM1) and molecules involved in B-T cell interactions (CD80, CD86, MHC-II) [14, 15].

In nodular lymphocyte predominant HL (NLPHL), the HRS cells are mononuclear with convoluted and lobulated nuclei and hence called popcorn or lymphocytic and histiocytic cells. They lack non-B cell antigens CD30 and CD15 and express CD45, CD20, and B-lineage antigens.

Diagnostic work-up should include

- Clinical evaluation with a detailed history and physical examination: All the lymph node regions including the Waldeyer's ring should be examined and their sizes documented. An ENT examination should be sought in case of suspicious involvement of Waldeyer's ring as involvement is based on clinical judgment rather than imaging in this scenario.
- Laboratory investigations:
  - Complete blood counts (CBC) and differential leukocyte counts and erythrocyte sedimentation rate (ESR)
  - Lactate dehydrogenase (LDH), liver function tests (LFT), and serum creatinine
  - Beta 2 microglobulin
  - Coagulation tests
  - Baseline viral screening (HBsAg, HIV, anti-HCV)
  - Baseline IgG levels
- Chest X-ray: An upright posterior-anterior chest X-ray (bulky mediastinal disease is as defined in the section on staging below).
- Ultrasonography (USG) abdomen to look for splenic lesions in case of doubt on PET-CT.
- F^{18} FDG positron emission tomography-computerized tomography (PET-CT) to stage the disease. This modality combines functional and anatomic characteristics and is used for staging and monitoring the disease [16–18].
- The five-point scale also referred to as the Deauville criteria [19, 20], which is a visual PET criteria, has been used for baseline staging and response assessment, with mediastinal blood pool utilized as the reference activity in baseline and late response assessment scans and liver blood pool being utilized in early response assessment scans. The five-point scale is as follows:
  - Score 1—no uptake
  - Score 2—uptake less than or equal to the mediastinum
  - Score 3—uptake greater than the mediastinum, but less than the liver
  - Score 4—uptake moderately higher than the liver
  - Score 5—uptake markedly higher than the liver
  - For baseline staging, FDG PET positivity is defined as scores three, four, and five. For response assessment scores four and five are considered positive
- Bone marrow aspiration and biopsy: If PET-CT is not available, bone marrow studies are to be done for those with B symptoms or Stages III and IV. PET-CT has high sensitivity (96.9%) and specificity (99.7%) in detecting bone marrow involvement at baseline, with focal involvement highly predictive of marrow involvement [21].
- Bone scan: Is indicated if PET-CT is not available and the child has bone pains, otherwise unexplained elevated alkaline phosphatase.
- CT (computerized tomography)/MRI (magnetic resonance imaging) of neck, chest, abdomen, and pelvis—if PET-CT is not available.
- Echocardiography (optional).
- Fertility preservation is recommended wherever feasible
  - Sperm cryopreservation in post-pubertal boys
  - Oophoropexy in girls if considered for pelvic radiotherapy

4.3 Assessment of Involved Regions and Staging

HL spreads by contiguous lymph node spread, which is the basis of the Ann Arbor staging system [22, 23] described in Table 1.

4.4 Risk Stratification

Disease risk assignment varies among the different trial groups [24] as is shown in Table 2. Broadly risk groups are assigned as low-risk intermediate and high risk based on stage, presence of B symptoms, involvement of extra-nodal sites, and presence or absence of bulky disease. Elevated ESR is a risk factor in the EuroNet consortium.

Table 1 The sub-stage classifications A, B, E, S, and X amend each stage based on defined features [22, 23]

Stage I	Involvement of a single lymphatic site (i.e., nodal region, Waldeyer's ring, thymus, spleen) (I); or localized involvement of a single extra lymphatic organ or site in the absence of any lymph node involvement (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extra lymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by extra lymphatic extension in association with adjacent lymph node involvement (IIIE) or by the involvement of the spleen (IIIS) or both (IIIE, S)
Stage IV	Diffuse or disseminated involvement of one or more extra lymphatic organs, with or without associated lymph node involvement; or isolated extra lymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow, lungs (not E), or cerebrospinal fluid

B, B symptoms; A, absence of B symptoms; S, spleen involvement; E, extra-nodal extension, which most commonly involves lung, pleura, pericardium, or bone when there is contiguous extension of lymph node disease or the site is proximal to an involved draining lymph node. X, the bulky disease is defined differently by various study groups. Bulky peripheral lymphadenopathy is defined as a single or conglomerated lymph nodal mass >6 cm in longest diameter. The bulky mediastinal disease is defined as a mediastinal mass with a horizontal tumor diameter ≥1/3rd the thoracic diameter. EuroNet study protocol utilizes nodal volume ≥200 mL as measured on CT scan to define bulky disease

Table 2 Disease risk assignment by various pediatric Hodgkin lymphoma study groups [24]

Group	Risk	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
Children's Oncology Group (COG)	LR								
	IR	E X		E X					
	HR								
EuroNet-PHL-C1	TG1-LR								
	TG2-IR	E RF	E RF	E RF					
	TG3-HR				E	E			
EuroNet-PHL-C2	TL1-LR								
	TL2-IR	E RF	E RF	E RF					
	TL3-HR				E	E			

LR low risk, *IR* intermediate risk, *HR* high risk, *TG* treatment group, *TL* treatment level, *E* extranodal involvement, *RF* risk factors defined as ESR ≥30 mm/h and/or ≥200 mL volume in nodal or mediastinal mass

5 Principles of Management

Treatment of cHL has evolved over the decades from single modality approaches utilizing high-dose radiation and multi-agent chemotherapy to combined modality treatment incorporating chemo-radiotherapy. The burden of late effects of treatment in childhood HL survivors led to successive trials employing strategies to curtail therapy. Risk-adapted, gender-based, response-based protocols have a common aim of tailoring therapy maintaining excellent cure rates while minimizing toxicity.

6 Medical Management

The frontline treatment of cHL utilizes chemotherapy and radiotherapy.

6.1 Chemotherapy

Current multidrug regimens incorporate non-cross-resistant drugs with different mechanisms of action and non-overlapping toxicities. Initial regimens like MOPP had alkylating agents like mechlorethamine with higher leukemogenicity which led to its substitution with cyclophosphamide and development of COPP. But the permanent gonadal toxicity due to gonadotoxic alkylating drug, procarbazine led the way to the development of ABVD and non-alkylating agent-based regimens like VAMP and OEPA [25]. ABVD or derived hybrid combinations are used in many countries for low-risk diseases with the addition of other agents to intensify therapy for intermediate and high-risk diseases, but cardiopulmonary toxicity related to the use of anthracyclines and bleomycin is a potential concern. Chemotherapy regimens used in German DAL-GPOH-HD studies have evolved from OPPA/COPP to the OEPA/COPDac regimens used in EuroNet-PHL trials replacing procarbazine with etoposide and dacarbazine with reduced leukemogenicity and gonadotoxicity [26].

6.2 Radiotherapy (RT)

RT in the treatment of HL has been employed either singly or in combination with chemotherapy.

The use of radiotherapy in HL has evolved from the standard mantle field to involved field radiotherapy (IFRT) and involved site radiotherapy (ISRT), more so with the current combined modality approach. This together with modern imaging and delivery techniques for better conformal dosing has significantly contributed to reducing end-organ toxicity and sequelae.

The risk-adapted approach has helped in the delivery of graded intensity of RT across risk groups without compromising outcomes. The sites of delivery of RT are also variable across groups ranging from irradiating all initially involved nodal regions to only those with baseline bulky disease or poor response to initial chemotherapy.

Recent trials have shown that interim response assessment incorporating functional imaging in addition to anatomic considerations is a better and more sensitive tool in selecting patients for the avoidance of RT. Rapid early responders or those with adequate response could select patients in whom RT was avoided without compromising outcomes (details of trials in the response assessment section below). These trials have also shown that such a response-based strategy requires an intensive chemotherapy backbone.

7 Monitoring According to Risk Stratification

7.1 Response Assessment

Contemporary trials use response assessment after a few cycles of chemotherapy to define treatment duration and the need for radiation. Definitions for response assessment are variable across different protocols and have utilized CT scans for size reductions and/or functional imaging to assess activity by FDG-PET or Gallium scans.

7.1.1 Early Response Assessment (ERA)

Table 3 lists some of the trials that have used ERA for therapy titration.

Various regimens used for the treatment of HL are detailed in Table 4 (low-risk HL), Table 5 (intermediate-risk HL), and Table 6 (high-risk HL).

If there is persistent PET-positive disease at the end of the prescribed regimen or progression of the disease, a histological diagnosis is needed to confirm the presence of HL. Seldom a progressive disease or refractory disease is actually an infection like tuberculosis.

Table 3 Response assessment and therapy modification as per various Hodgkin's Lymphoma Study Groups

Group	Stage	Response criteria	Therapy modification	Survival rates
Pediatric Oncology Group (POG) [27]	Intermediate and advanced	*CT and Gallium scan after 3 cycles ABVE-PC*: RER: ≥50% reduction in SPPD and negative Gallium scan SER: Failure to achieve RER	RER: IFRT SER: 2ABVE-PC + IFRT	5-year EFS RER: 86% SER: 83%
Children's Cancer Group (CCG) [28]	High risk	*CT and Gallium scan after 4 cycles eBEACOPP*: RER: ≥70% reduction in size and Gallium negativity and resolution of B symptom SER: Failure to achieve RER	RER: Females: 4COPP/ABV, no IFRT Male: 2ABVD + IFRT SER: 4eBEACOPP + IFRT	5-year EFS (Overall): 94% 5-year OS: 97%
EuroNet-PHL-C1 [26]	All risks	*PET-CT done after 2 cycles OEPA*: Adequate response: ≥50% reduction in size with PET negativity (Deauvilles1,2,3) or complete resolution regardless of PET Inadequate response: Failure to achieve adequate response	Adequate response: TG1: no chemo TG2: 2COPDac TG3: 4COPDac + no IFRT Inadequate response: (TG2: 2COPDac TG3: 4COPDac) + IFRT	Results not published
Pediatric Hodgkin Consortium [29]	Low risk	*CT scan and Gallium/PET scan after 2VAMP*: CR: ≥75% reduction in SPPD and negative Gallium/PET	CR: 2VAMP + no IFRT <CR: 2VAMP + IFRT	5-year EFS CR: 89% <CR: 88%
COG [30]	Intermediate risk	*CT scan after 2 ABVE-PC* *In RER, CT scan + Gallium/PET after 4 ABVE-PC also to assess CR*: RER: ≥60% reduction in size SER: Failure to achieve RER CR: ≥80% reduction in size and negative Gallium/PET	RER + CR: ±IFRT RER + <CR: +IFRT SER: [2ABVE-PC/(2DECA + 2ABVE-PC)] + IFRT	3-year EFS RER + CR: +IFRT: 88% −IFRT: 85% (p-0.07) SER: +DECA: 80% −DECA: 75% ($p > 0.05$)

ABVE-PC doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide, *OEPA* vincristine, etoposide, prednisolone, doxorubicin, *COPDac* cyclophosphamide, vincristine, prednisolone, dacarbazine, *eBEACOPP* bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine, *COPP/ABV* cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, *DECA* dexamethasone, etoposide, cisplatin, cytarabine, *ABVD* doxorubicin, bleomycin, vinblastine, dacarbazine, *VAMP* vinblastine, doxorubicin, methotrexate, prednisone, *SPPD* sum of the product of perpendicular diameters, *RER* rapid early responder, *SER* slow early responder

Table 4 Protocols for management of low-risk Hodgkin lymphoma

Group	Stage	Chemotherapy	RT (Gy)	EFS (%)	OS (%)
Stanford, St Jude, Dana-Farber [29]	I/II	4VAMP	IFRT (15–25.5)	10 years: 89	10 years: 96
	I/II	4VAMP	CR after 2VAMP: None PR-IFRT (25.5)	5 years: 89 5 years: 88	10 years: 100
CCG [31]	IA/IB/IIA	4COPP/ABV	CR after 4 cycles: None/IFRT (21)	10 years: 89 10 years: 100 (*p*-0.004)	10 years: 96 10 years: 97 (*p*-0.50)
POG [32]	IA/IIA/IIIA without bulky disease	2–4DBVE (based on the response after cycle 2)	CR after 2 cycles: IFRT (25.5) PR-IFRT (25.2)	6 years: 91	6 years: 98
GPOH-HD 95 [33]	I/IIA	2OEPA/OPPA	CR after 2 cycles: None PR-IFRT (20–35)	5 years: 97 5 years: 94	5 years: 99.5
COG [34]	IA/IIA without bulky disease	3AV-PC	CR after 3 cycles: None PR-IFRT (21)	4 years: 79.9	4 years: 99.6

DBVE doxorubicin, bleomycin, vincristine, etoposide, *AV-PC* doxorubicin, vincristine, prednisone, cyclophosphamide

Table 5 Protocols for management of intermediate-risk Hodgkin lymphoma

Group	Stage	Chemotherapy	RT (Gy)	EFS (%)	OS (%)
CCG [31]	I/II[a]/IIB/III	6COPP/ABV	CR after 6 cycles: None/IFRT (21)	10 years: 78 10 years: 84[b]	3 years: 100
COG [30]	IB/IAE/IIB/IIAE/II/IVA/IA, IIA with bulky disease	CT scan after 2 ABVE-PC In RER, CT scan + Gallium/PET after 4ABVE-PC also to assess CR SER: ±DECA + 2ABVE-PC	RER, CR: ±IFRT RER, <CR: +IFRT SER: IFRT	3 years RER, CR +IFRT: 88 None: 85 (*p*-0.07) SER: DECA-80 No DECA-75 ($p > 0.05$)	4 years: 99.6
EuroNet-PHL-C1 [26]	TG-2	2OEPA+ 2COPDac	Adequate response: None Inadequate response: IFRT	NP	NP

NP not published

[a] Adverse features

[b] As treated analysis

Table 6 Protocols for management of high-risk Hodgkin lymphoma

Group	Stage	Chemotherapy	RT (Gy)	EFS (%)	OS (%)
CCG [28]	IIB/IIIB/IV	*CT and Gallium scan after 4 cycles eBEACOPP:* RER: Females: 4COPP/ABV Male: 2ABVD SER: 4eBEACOPP	RER: Females: No IFRT Male: IFRT (21) SER: 4eBEACOPP + IFRT (21)	5 years: 94	5 years: 97
POG [27]	IIB/IIIB/IV	*CT and Gallium scan after 3 cycles ABVE-PC:* RER: No chemo SER: 2ABVE-PC	RER: None SER: IFRT	5 years RER: 86% SER: 83%	5 years: 95
EuroNet-PHL-C1 [26]	TG-3	2OEPA+ 4COPDac	Adequate response: None Inadequate response: IFRT	NP[a]	NP[a]

[a] *NP* not published

Table 7 Protocols for management of nodular lymphocyte predominant Hodgkin lymphoma

Group	Stage	Chemotherapy	RT	EFS (%)	OS (%)
UK [39]	I completely resected	None	None		
	I incompletely resected/II	3CVP	None	5 years: 74	5 years: 100
COG [40]	IA completely resected	None	Nil	3 years: 82	5 years: 100
	IA unresected/IIA	3AV-PC	CR: None <CR: 21 Gy IFRT	5 years: 85.5	
Stanford, St Jude, Dana-Farber [29, 41]	I/II	4VAMP	None IFRT (25.5 Gy)	5 years: 89.4 5 years: 85.7	5 years: 100
	I/II	4VAMP	IFRT (15–25.5 Gy)	5 years: 100	5 years: 100

CVP cyclophosphamide, vinblastine, prednisolone

8 Nodular Lymphocyte-Predominant HL (NLPHL)

NLPHL has traditionally been included in the HL trials, though now they are separately studied due to their different clinico-immunophenotyping characteristics and behavior with excellent outcomes in limited disease warranting an approach different from cHL.

- NLPHL comprises 5–8% of childhood HL, with a higher proportion of prepubertal patients with significant male preponderance compared to cHL [35].
- A more indolent disease with a higher proportion of low-stage disease, mostly presenting as localized adenopathy in the neck. Mediastinal involvement is rare. Non-contiguous lymph node involvement can be observed in higher disease stages [36].
- Late and multiple relapses occur.
- There is an increased risk of transformation to NHL in up to 5–12% of cases [37].
- Histologically, there is effacement of lymph-node architecture with nodular lymphocyte infiltrates with scatted L&H cells or popcorn cells that express CD45, CD20, CD79a, and other normal B-cell antigens and are negative for CD15 and CD30. L&H cells are also EBV-negative [38].
- Given the favorable outcomes in those with a limited disease where major events are due to side effects of therapy, this less intensive strategy is implemented in contemporary treatment protocols. Completely resectioned stage IA can be observed alone and unresected stage IA/IIA can be treated with less intense chemo with RT only for those with poor response. Table 7 summarizes the options available.

Higher stages of the disease have better outcomes when treated on cHL regimens. A retrospective evaluation of treatment outcomes in advanced NLPHL from the UK and France which incorporated rituximab into multi-agent chemotherapy showed reasonable outcomes [42]. There are not many published studies from India, except the report from Tata Memorial Hospital which showed favorable outcomes despite unfavorable presentations in a heterogeneously treated cohort [43].

9 Management of Relapsed and Refractory HL

Relapse in HL has a realistic chance of cure prognostic factors including time to first relapse (most important), inadequate response to initial second-line treatment, stage at relapse, extra-nodal relapse, and a number of relapses. All relapses should be confirmed by biopsy and should be restaged using PET-CT. There is no survival benefit in routine surveillance by imaging in HL.

Treatment options are presented in Table 8.

Table 8 Salvage therapy options for relapsed Hodgkin lymphoma

Chemotherapy	Recommended second-line therapy, with the choice of drugs and schedule decided by previous therapy and initial response to these agents. Various regimens used include • ICE (ifosfamide, carboplatin, and etoposide) [44] • IEP/ABVD (ifosfamide, etoposide, prednisone/doxorubicin, bleomycin, vinblastine, dacarbazine) [45] • Ifosfamide and vinorelbine with or without bortezomib [46] • IGEV (ifosfamide, gemcitabine, vinorelbine) [47] • GDP (gemcitabine, dexamethasone, cisplatin) [48] • MINE (mitoxantrone, ifosfamide, vinorelbine, etoposide) [49] • Bendamustine [50]
Targeted therapy	Targeted therapy available includes • Rituximab either alone or combined with chemotherapy in CD20-positive relapses [51] • Brentuximab vedontin (Bv), anti-CD30 antibody linked to cytotoxic monomethyl auristatin-E (MMAE)
Checkpoint inhibitor therapy	These block the interaction between programmed death-1 (PD-1) and its ligands. Anti-PD-1 antibodies include: • Nivolumab (objective response: 87%) • Pembrolizumab (objective response rate of 65%)
Hematopoietic stem cell transplantation (HSCT)	Patients with refractory/early relapse, multiple relapses, and prior treatment with intensive chemo-radiotherapy respond poorly to conventional salvage therapy and have better remissions with myeloablative therapy followed by HSCT. Several studies report survival rates ranging from 30% to 60% [52–54]. Refractory/early relapse and PET positivity prior to transplant are risk factors for failure. Auto-SCT (mostly following BEAM [BCNU, etoposide, cytarabine, melphalan] conditioning) is the first choice in most centers. Reduced intensity conditioning (RIC) utilizing fludarabine or low-dose total body irradiation followed by allogenic-SCT is indicated if: • Relapse within 6 months of a prior autologous HSCT • Chemo-refractory disease (PET positivity after initial chemotherapy) • Bone marrow involvement at relapse
Radiotherapy	In sites not previously irradiated, RT can be used to enhance local control In sites not responsive to salvage therapy RT may be administered prior to HSCT
Novel agents	Novel agents under investigation include • Adoptive immunotherapy—autologous cytotoxic T lymphocytes (CTLs) against EBV antigens in cHL associated with EBV • Epigenetic therapies, such as the histone de-acetylase (HDAC) inhibitors like panobinostat

10 Late Effects

Late effects have their own significance in HL. Even though 5-year survival rates in HL are in excess of 90%, it steadily declines in the later years both due to relapse and late effects. Both chemotherapy (especially alkylating agents, anthracyclines, and bleomycin) and radiotherapy significantly, impair quality of life. The successive trials have adopted risk, gender, and response-based strategies to refine and tailor therapy to avoid many of these late effects. The following sections present the main late effects seen in HL survivors.

10.1 Cardiac Toxicity

Cardiac toxicity is mainly caused by anthracyclines and radiation exposure to the heart [55, 56].

Anthracycline-induced toxicity can manifest as subclinical left ventricular dysfunction, cardiomyopathy, or congestive heart failure.

Radiation-induced damage can lead to subclinical left ventricular dysfunction cardiomyopathy, pericarditis, heart valve dysfunction, conduction disorders, coronary, carotid, subclavian vascular disease, and myocardial infarction.

Strategies employed in the prevention of anthracycline cardiotoxicity include

- decrease cumulative anthracycline exposure
- use of analogs with less cardiotoxicity
- use of liposomal doxorubicin
- use of cardioprotectants like dexrazoxane
- drugs like angiotensin-converting enzyme inhibitors and beta blockers have only a transient effect
- pharmacogenomic led dosing
- risk factor (obesity, hypertension, diabetes, hyperlipidemia) prevention and treatment
- lifestyle modifications

10.2 Pulmonary Toxicity

Radiation, bleomycin, and HSCT contribute to pulmonary toxicity [57].

Radiation leads to pulmonary fibrosis, interstitial pneumonitis restrictive lung disease, and obstructive lung disease.

Bleomycin can cause interstitial pneumonitis pulmonary fibrosis ARDS and rarely pulmonary veno-occlusive disease. Patients who undergo HSCT in the relapse setting are at risk of bronchiolitis obliterans organizing pneumonia (BOOP), restrictive lung disease, and obstructive lung disease.

10.3 Thyroid Abnormalities

These include the following and are radiation-induced [58].

Radiation exposure leads to thyroid disorders and can manifest as hypo or hyperthyroidism. Risk factors include increasing radiation dose, female sex, and older age at diagnosis. The Childhood Cancer Survivor Study reported a 20-year actuarial risk of 30% in survivors treated with 35–44.9 Gy and 50% at doses ≥45 Gy. Develops most often in the first 5 years after treatment but can be seen up to 20 years. Annual TSH level monitoring is recommended if elevated and lifelong replacement therapy might be required.

Hyperthyroidism is seldom seen at high doses of radiation exposure.

Patients might also develop thyroid nodules. High radiation exposure and female sex are risk factors. Persistent and enlarged nodules require USG and periodic FNAC. The risk of thyroid cancer is 18-fold as compared to the general population.

10.4 Gonadal Toxicity

Alkylating agents predispose to gonadal toxicity. In males, high incidence of testicular dysfunction in alkylating agents, especially procarbazine-based regimens leading to its substitution with other agents (etoposide and dacarbazine in GPOH trials). Azoospermia is the main effect of preserved hormonal function. Hence sperm cryopreservation is to be discussed with post-pubertal boys before therapy initiation.

In females, if pelvic radiation is required ovaries can be transposed away from the radiation field premature menopause rates approach 3.8% for those who received pelvic radiation and alkylating agents.

10.5 Subsequent Neoplasms (SMN)

Fifteen-year cumulative incidence of secondary acute myeloid leukemia was 1% in DAL-HD studies when procarbazine was the alkylating drug. Drugs like etoposide and cyclophosphamide are also associated with sAML mostly seen in the first 7 years after therapy, but most of the newer regimens use doses below the leukemogenic threshold.

Risk for NHL is also increased with an estimated 20-year cumulative incidence of 1.5% [59].

The cumulative risk for the DAL/GPOH-HD study patients has been 5.7% after 20 years and increased to 11% after 22 years. The OS has been 94% after 20 years and dropped to 87% after 24 years.

In the study by the American Late Effects Study Group (LESG), the rate of secondary tumors increased steeply between 20 and 30 years. After 30 years the rate of secondary malignant tumors approached 25% mainly contributed by secondary solid tumors (SST) [59]. The main culprit for the development of SST is radiation therapy, and subsequently, modification of fields and doses have been attempted to reduce this late effect. However, one recent study indicated that a reduction in RT dose from 36–44 to 15–25 Gy may not significantly decrease the risk of second tumors.

10.6 Growth and Development

Growth retardation was seen more with previous regimens, which delivered high-dose axial skeleton radiation. The newer techniques employing lower doses and IFRT have significantly reduced this problem. Hypothyroidism may contribute to this late effect post-RT. Obesity and metabolic syndrome are concerns that have been recently noted to be on an increase in survivors.

11 Treatment Algorithms Used in Tata Memorial Hospital (TMH)

Step 1. Biopsy-proven treatment naïve cHL is staged using PET-CT

Step 2. Risk stratification is done as per Table 9

Step 3. The treatment algorithm is presented in Fig. 1

Table 9 Tata Memorial Hospital risk assignment strategy for classical Hodgkin lymphoma

Group	Risk	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
TMH	LR								
	IR	X	X	X E					
	HR				E X	E X			

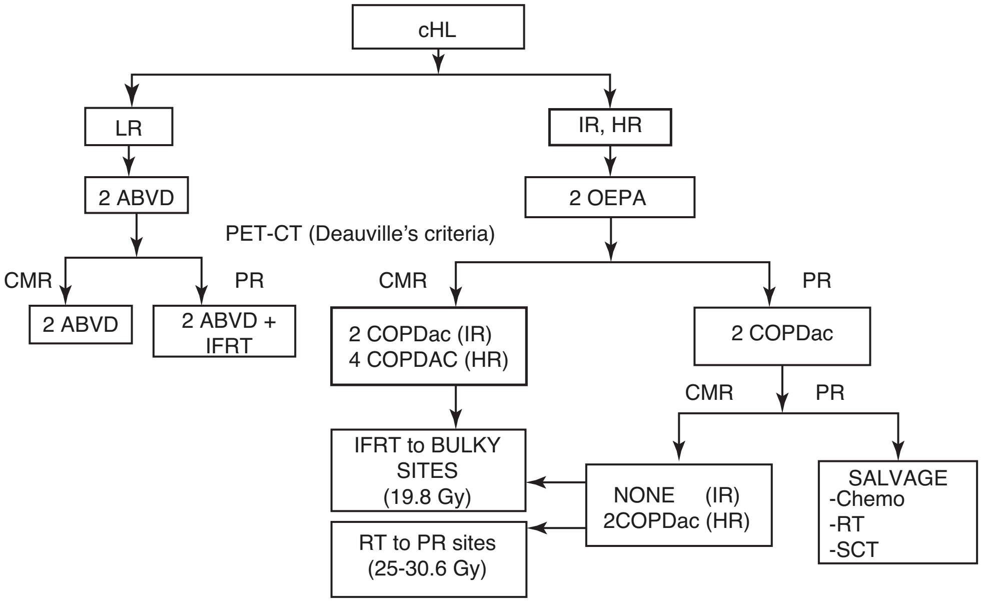

Fig. 1 In India, HL has conventionally been treated on a less intensive protocol utilizing ABVD and IFRT across all stages, with recent few protocols utilizing response-based RT across all stages. The only randomized controlled trial from India comparing combined modality treatment vs chemotherapy alone based on response assessment at the end of chemotherapy showed that consolidation radiation in those achieving complete response improved 8-year EFS (97% vs 53%, *p*-0.02) and OS (100% vs 89%, *p*-0.04) [60]. Intensifying primary chemotherapy has been shown to better select patients in whom RT can be avoided if rapid early response is obtained. The decision of continued application of RT to baseline bulky sites even in CMR on ERA despite being on an intensive chemotherapy backbone was taken in the institute considering the limited salvage options available to the population catered to. Even though relapse in HL provides a realistic chance of cure, brentuximab, nivolumab, and hematopoietic transplantation are not feasible options in the majority. A randomized controlled trial addressing the renunciation of RT even to bulky sites based on earl response assessment is being contemplated in a multi-centric fashion to allow solid evidence for the same

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Pediatric Myeloproliferative Disorders/Myelodysplastic Syndromes/Overlap Syndromes

Vasudeva Bhat K and Hemani Jain

Abbreviations

AMKL	Acute megakaryoblastic leukemia
AML	Acute myeloid leukemia
DS	Down syndrome
JMML	Juvenile myelomonocytic leukemia
MDS	Myelodysplastic syndromes
MPN	Myeloproliferative neoplasms
MSD	Matched sibling donor
RAEB	Refractory anemia with excess of blasts
RAEBt	Refractory anemia with excess of blasts in transformation
RC	Refractory cytopenia
TAM	Transient abnormal myelopoiesis
UD	Unrelated donor

1 Introduction

Myeloproliferative neoplasm [MPN]/Myelodysplastic syndrome (MDS) overlap syndrome are disorders that have concurrent proliferative as well as dysplastic changes. MDS is characterized by anemia, leucopenia and thrombocytopenia in peripheral blood, dysplasia of various cell lineages in bone marrow, genetic anomalies and a high risk of progression to leukemia [1]. Clonal expansion of one or more hematopoietic cell lineages in the bone marrow, extramedullary infiltration in liver and spleen, and constitutional symptoms define MPN. There are various differences between adult and pediatric MDS, mainly in their clinical presentation and the cytogenetic abnormality associated with it. World Health Organization (WHO) 2003 and 2008 classification for pediatric MDS comprises three major diagnostic categories, as depicted below [2, 3].

1. Myelodysplastic/myeloproliferative disorders includes juvenile myelomonocytic leukemia (JMML), secondary chronic myelomonocytic leukemia (CMML) and *BCR::ABL1* negative chronic myeloid leukemia (Ph− CML)
2. Myeloid leukemia of Down syndrome (DS): includes transient abnormal myelopoiesis (TAM) and AML in children with DS
3. MDS includes the subtypes: refractory cytopenia (RC) with <2% blasts in PB and <5% blasts in BM, refractory anemia with excess blasts (RAEB) presents with 2–19% blasts in PB and 5–19% blasts in BM, and RAEB in transformation (RAEB-t) in children present with 20–29% blasts in PB or BM.

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2 Incidence and Epidemiology in India and Globally

The incidence of pediatric MDS is lesser than 5% of all hematological malignancies [3]. Compared to adult MDS, the annual estimated incidence reported in childhood MDS is 0.5–4 per million and is typically detected in males under the age of 8; however, it can be diagnosed between the ages of 6 and 8 years, but with a male predominance. However, JMML (juvenile myelomonocytic leukemia) is commonly diagnosed in children with a median age presentation of 2 years. Since pediatric MDS is rare and difficult to diagnose, epidemiological data for pediatric MDS is limited. Several case series of pediatric MDS have been reported [4–12]. Sasake et al. [4] retrospectively analyzed 189 MDS patients less than 16 years old from 62 centers in Japan over 7 years. Tilak et al. [13] from northern India reported 19 cases of pediatric MDS with ages ranging from 3.5 to 16 years.

3 Clinical Presentation

Morphology, cytogenetics and prognosis differ significantly in adult and pediatric MDS. Anemia, bleeding and infection are the most prevalent symptoms in adult MDS patients, while fever secondary to neutropenia and bleeding due to thrombocytopenia are prominent in juvenile MDS patients. Constitutional and genetic disorders are strongly associated in 50% of MDS patients, as shown in Table 1; hence, screening for syndromic features like short stature, microcephaly, etc. is also very important in children.

Table 1 Predisposing conditions for childhood MDS [1]

Constitutional conditions
Congenital bone marrow failure
• Fanconi anemia
• Kostmann syndrome
• Shwachman–Diamond syndrome
• Blackfan–Diamond anemia
Trisomy 8 syndrome
Familial MDS (at least one first-degree relative with MDS/AML)
Associated conditions
• Prior chemotherapy/radiation, aplastic anemia

4 Evaluation and Work-Up Including Risk Stratification

4.1 Juvenile Myelomonocytic Leukemia (JMML) and Other Myelodysplastic/Myeloproliferative Disorders

Majority (>95%) of JMML cases are usually detected before the age of 4 with an annual incidence of roughly 4 per million. Currently used diagnostic criteria have been published [14, 15] (Table 2). Absolute peripheral blood monocytosis ($>1 \times 10^9$/L), presence of <20% blasts in peripheral blood or bone marrow, hepatosplenomegaly and absence of Philadelphia chromosome (*BCR::ABL1* fusion) are mandatory. JMML patients may present with bleeding, cough, pallor, fever, infection, poor weight gain, rash, leukocytosis, anemia, thrombocytopenia and elevated HbF. A bone marrow aspiration is required to rule out acute myelomonocytic leukemia, AML M4. Granulocytic cells are predominantly found at all stages of maturation with a hypercellular marrow. Monosomy 7 is seen in 25% of cases, random cytogenetic aberrations in 10% cases and 65% cases show a normal karyotype [15, 16]. Early and accurate diagnosis plays an important role in decision of therapy including stem cell transplant.

The newer diagnostic guideline for JMML recommends and incorporates molecular testing as depicted below in Table 3.

Table 2 Diagnostic guidelines for JMML [14, 15]

Suggestive clinical features	Hepatosplenomegaly
	Lymphadenopathy
	Pallor
	Skin rash
Laboratory criteria	No Ph chromosome, no BCR:ABL1 fusion
Minimal criteria (All 3 must be fulfilled)	PB monocyte count $>1 \times 10^9$/L
	Bone marrow blast count <20%[a]
Criteria for definite diagnosis (At least 2 must be fulfilled)	Hemoglobin F increased for age
	Myeloid precursors in blood smear
	White cell count $>10 \times 10^9$/L
	Clonal abnormality
	GM-CSF hypersensitivity of myeloid progenitors

[a] BM blasts may occasionally be 20–30% in an otherwise typical JMML.

Table 3 Latest diagnostic guidelines for JMML 2016 revision to World Health Organization Classification

Clinical and hematologic features (All are needed)	Absence of the BCR::ABL1 fusion
	$>1 \times 10^9$/L circulating monocytes
	<20% blasts in the peripheral blood and bone marrow
	Splenomegaly
Genetic studies (Any 1 is needed)	Somatic mutation in KRAS, NRAS, or PTPN11
	Clinical diagnosis of NF1 or NF1 gene mutation
	Germline CBL mutation and LOH of CBL
Other features if genetic testing not available (Along with clinical and hematological features)	Monosomy 7 or other chromosomal abnormality OR
	At least 2 of the below
	– Circulating myeloid or erythroid precursors
	– Increased hemoglobin F for age
	– Hyperphosphorylation of STAT5
	– GM-CSF hypersensitivity

CMML is included in the categorization; however, it is used only for cases that occur as a result of previous chemotherapy. In children, BCR::ABL1-negative chronic myeloid leukemia, included in the group of myelodysplastic/myeloproliferative disorders, is exceedingly rare, and presumably, the majority of cases are JMML.

Neurofibromatosis type I (NF-1) and Noonan syndrome (NS) are inherited diseases susceptible to develop JMML. Neurofibromatosis is found in about 14% of JMML cases with NF1 gene mutation in 30% of cases [17]. Children with Noonan syndrome (NS) are at very high risk of developing JMML or a myeloproliferative disorder (MPD). Mutations like CBL, KRAS, NRAS, NF1 and PTPN11 are present in about three-fourth of cases of JMML, while the remaining one-fourth of cases probably harbor unidentified mutated genes [18]. It is of paramount importance to define whether these mutations are somatic or germline as that determines the therapy.

4.2 Myeloid Leukemia of Down Syndrome (ML-DS)

Presence of constitutional trisomy 21 in patients with Down syndrome (DS) increases the risk of developing ML-DS by 150 folds. Acute leukemia is preceded by transient abnormal myelopoiesis (TAM), a neonatal clonal preleukemic syndrome that is unique to Down syndrome [19, 20].

4.3 Transient Abnormal Myelopoiesis (TAM)

TAM affects 4% to 10% of newborns with Down syndrome. It normally starts during fetal and neonatal life and disappears in 2–14 weeks, although 20% to 30% of cases advance to acute megakaryoblastic leukemia (AMKL) in 1–3 years. Blasts are morphologically and immunophenotypically similar to megakaryocytic lineage. Early mortality is seen in 17% of TAM patients due to leukocytosis, elevated bilirubin and liver enzymes [21].

GATA1 mutations and JAK-STAT pathway alterations are seen in both TAM and myeloid leukemia associated with Down syndrome, with more mutations in myeloid leukemia patients.

4.4 Refractory Cytopenia (RC)

Among the various subtypes of MDS, RC is the most common subtype accounting for approximately half of all MDS cases [15]. It is characterized by less than 5% blasts in BM, less than 2% blasts in PB and dysplasia in more than one lineage. A trephine biopsy is compulsory to differentiate between hypoplastic MDS from aplastic anemia (AA). The biopsy in hypoplastic MDS shows sparse granulopoietic cells which are scattered, islands of immature erythropoiesis with a patchy appearance and in most cases, decreased megakaryopoiesis or micromegakaryocytes [22]. Detection of monosomy 7, by conventional karyotyping, indicates poor prognosis. The usual time to progression for children, with monosomy 7 with RC to advanced MDS, is less than 2 years [23].

4.5 Advanced Pediatric MDS

The morphology and blast count in the BM is used to classify advanced pediatric MDS. Advanced pediatric MDS is divided into two groups by the WHO: (1) RAEB-1 (5–10% blasts) or RAEB-2 (11–19% blasts) and (2) RAEB-t (20–29% blasts). Morphology and immunohistochemical features of pediatric RAEB and adult are similar. However, blood counts remain stable in children for a long time. Transformation from MDS to AML occurs in 30% of pediatric MDS within 2 years of diagnosis [24, 25].

The most prevalent chromosomal aberration occurring in 30% of pediatric MDS is monosomy 7 conferring poor prognosis. These patients have a dismal outcome with standard therapy irrespective of the number of blasts in the BM. Abnormal karyotype has been found in 30–50% of pediatric MDS, and most of them show numerical abnormalities. Only 10% show structural abnormalities [26].

4.6 Principles of Management of MDS

Allogeneic stem cell transplant has remained the most definitive option for treatment of MDS and the majority of JMML as it is a clonal disorder of hematopoietic stem cells. The therapy has evolved over time and is derived from adult MDS patients. Unlike adults, in children, the aim of therapy is curative rather than palliative. Modern treatment using farnesyl transferase inhibitors, antiangiogenic agents and methylation inhibitors used in adults has not shown benefit in pediatric age group. In the past, treatment was done using low-dose cytotoxic agents or differentiating agents; however, the outcomes with the above were dismal [27–29].

4.7 Refractory Cytopenia (RC)

The policy of wait and watch can be done only in children with refractory cytopenia (RC) who do not carry monosomy 7 or a complex karyotype and are neither transfusion dependent nor endangered by low neutrophil count. In such patients, periodic blood examination and bone marrow testing as indicated or yearly would suffice. In case of progressive disease, such children can then be referred to the transplant unit [23]. In those who are transfusion dependent or neutropenic, a transplant with a matched sibling or unrelated donor should be offered at the earliest with a probability of EFS being around 75% at 3 years. For patients with RC with no cytogenetic abnormality, conditioning regimens with reduced intensity have shown similar outcomes [30].

4.8 Advanced Primary MDS (RAEB/RAEB-t)

Cytoreductive therapy before proceeding to stem cell transplant is controversial. Few groups have included RAEB and RAEB-t as AML and have given therapy like AML. In such a group of patients, the expected results have been a remission rate of <60% with 5-year survival of <30% with plenty of relapses. Data from EWOG-MDS indicate that pretransplant chemotherapy did not improve survival, and the probability of survival after transplant was almost 50%. The outcomes were again not influenced by blast percentage in the bone marrow at the time of stem cell transplantation [31].

Patients can be transplanted either with a matched sibling, unrelated donor or haploidentical with almost similar outcomes [32–34]. Most of the study groups have used busulfan-based conditioning regimens with graft versus host disease prophylaxis being cyclosporine [35]. In the EWOG-MDS studies, the event-free survival at 5 years is 60% and approximately 40% for patients given stem cells from an MSD or an UD [31]. With the improvement in techniques of depleted grafts, it is possible, in future, that haploidentical transplants could also be a possibility, especially in scenarios where a match is not available.

4.9 Treatment of Secondary MDS

The probability of cure with allogeneic stem cell transplant in this group remains in the range of 20–30% overall survival in a few reported series [36]. The Children's Cancer Group (CCG) has reported better outcomes for intensive chemotherapy followed by stem cell transplantation compared to standard chemotherapy and transplant [37].

4.10 Principles of Management of JMML

JMML is a heterogeneous myeloproliferative disorder. It was previously treated like a MDS or leukemia; however, outcomes after therapy with these modalities have resulted in dismal outcomes. Cis-retinoic acid has shown durable remission in single-institution case series; however, there is no documented long-term survival with this single agent [38]. The most definitive therapy is stem cell transplant; however, in the era of molecular testing, few subsets of patients have been identified that do not mandate a stem cell transplant as described below [39].

4.11 Treatment of CBL Mutation

Patients carrying CBL mutation (≈15% of all cases) have congenital anomalies similar with those observed in neurofibromatosis 1. Children with germline CBL mutations develop JMML because of higher risk of having a loss of heterozygosity (LOH) for the CBL locus in progenitor stem cells. Majority of the children have self-resolving disease with only a few having a stormy clinical course. They often require only a low dose of short course of chemotherapy. Stem cell transplant is indicated only if the child progresses on wait and watch policy [39].

4.12 Treatment of Germline Mutation of KRAS/NRAS

In the EWOG MDS study, it was observed that children with germline RAS mutation with normal HbF levels and platelet counts had good outcomes without transplant; hence, these patients can be observed alone and planned for transplant if they progress.

4.13 Treatment of Somatic Mutation of KRAS/NRAS/PTPN11 and NF-1

Allogenic stem cell transplant is the only curative option for children with JMML associated with somatic mutations of KRAS/NRAS, NF-1 and PTPN11.

4.14 Principles of Management of TAM in Downs Syndrome

Majority of the neonates with TAM do not need any form of therapy and usually self-resolve over time [40]. Neonates with symptoms which are life-threatening like *hydrops fetalis*, hyperleukocytosis (WBC >100 × 10^9/L), liver dysfunction with DIC picture, kidney dysfunction or cardiac manifestations may benefit from lower doses of chemotherapy. The mortality rate reported for such symptomatic neonates is as high as 20% [41]. These children are extremely sensitive to cytarabine, and the recommended dose is 1 mg/kg for 3–12 days till symptom resolution.

A management algorithm for MDS is presented in Fig. 1, and a management algorithm for JMML is presented in Fig. 2.

4.15 Prognosis with Current Treatment

4.15.1 MDS

Outcomes with stem cell transplant in these patients have been reported between 50% and 73% in the literature. The key prognostic element is time to transplant, and outcomes with transplant posttransformation to AML are poor [31–35].

4.15.2 JMML

Prognosis with stem cell transplant in patients with JMML as reported by EWOG-MDS trial is 52% EFS and OS of 64% at 5 years [42]. The important prognostic factors in the study were age at transplant, gender and presence of cytogenetic anomalies. Age less than 2 years and male gender had superior outcomes. In the study, del (7q) had better outcomes compared to normal/other cytogenetic anomalies.

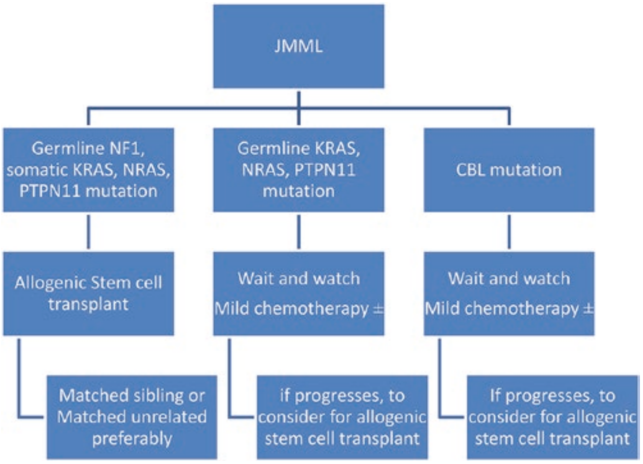
JMML
Germline NF1, somatic KRAS, NRAS, PTPN11 mutation
Germline KRAS, NRAS, PTPN11 mutation
CBL mutation
Allogenic Stem cell transplant
Wait and watch
Mild chemotherapy ±
Wait and watch
Mild chemotherapy ±
Matched sibling or Matched unrelated preferably
if progresses, to consider for allogenic stem cell transplant
If progresses, to consider for allogenic stem cell transplant

Fig. 2 Management algorithm for JMML

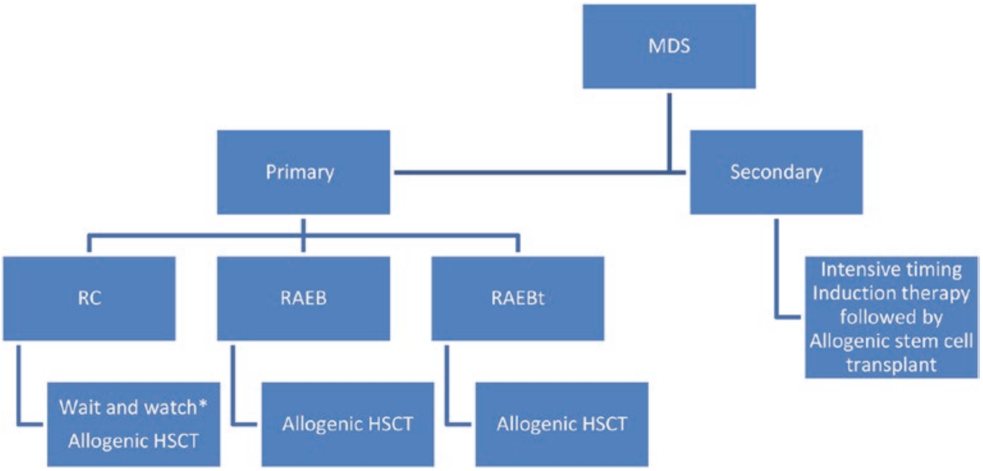
MDS
Primary
Secondary
RC
RAEB
RAEBt
Intensive timing Induction therapy followed by Allogenic stem cell transplant
Wait and watch*
Allogenic HSCT
Allogenic HSCT
Allogenic HSCT

Fig. 1 Management algorithm for MDS. *Wait and watch policy for RC with no monosomy 7/complex karyotype and nontransfusion-dependent/nonendangering neutropenia

4.16 Management of Recurrent Disease in Patients with MDS

Relapses following transplant in children with MDS is associated with a dismal outcomes. Salvage with donor lymphocyte infusions has occasionally been reported. Similar to most transplants in benign hematology, children with early relapse, detected by loss of chimerism or mixed chimerism, may need early withdrawal of the graft versus host disease prophylaxis and donor lymphocyte infusion, but they are at high risk of Graft versus host disease [43].

4.17 Management of Recurrent Disease in Patients with JMML

Repeat allogeneic stem cell transplant with same or alternate donor in patients with relapsed JMML has good outcomes. In the EWOG trial, 68 patients relapsed, out of which 26 had undergone a second transplant. The probability of 5-year disease-free survival in these patients was 32% [41].

5 How We Do It at TMC

In TMC, any child with suspected MDS/JMML is worked up as shown in Table 4.

Table 4 Work-up of child with suspected MDS/JMML

Evaluation

- Detailed history and clinical examination
- Complete blood count with manual differential counts
- Organ function testing
- Hemoglobin F levels
- Bone marrow evaluation with biopsy (aspirate for morphology, cytogenetics and molecular testing)
- Cytogenetics is processed for Monosomy 5/7, Ph chromosome and conventional karyotyping
- Testing for chromosomal fragility is done in suspicion of Fanconi anemia
- Molecular testing includes detection of KRAS, NRAS, PTPN11 and CBL mutation
- HLA typing of siblings and parents
- In a matched sibling, cytogenetic and molecular testing is done to rule out constitutional syndromes prior to transplant

Treatment

- To counsel for allogenic stem cell transplant
- Wait and watch for patients with refractory cytopenia (nontransfusion-dependent/nonneutropenic) and JMML with CBL mutation and germline KRAS/NRAS/PTPN mutation

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Hematopoietic Stem Cell Transplantation

Avinash Bonda and Navin Khattry

Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BM	Bone marrow
CML	Chronic myeloid leukemia
GVHD	Graft versus host disease
HD	Hodgkin's disease
HSC	Hematopoietic stem cell
KDR	Kinase domain receptor
MDS	Myelodysplastic syndrome
NA	Nucleoside analog
NHL	Non-Hodgkin's lymphomas
TBI	Total body irradiation
TLI	Total lymphoid irradiation

1 Introduction

Hematopoietic stem cell transplantation refers to the infusion of pluripotent stem cells, usually derived from bone marrow, peripheral blood or umbilical cord. It may be autologous (the patient's own stem cells are used), allogeneic (from a donor) or syngeneic (from an identical twin).

Stem cells are a population of undifferentiated cells capable of indefinite self-renewal and generation of a functional progeny of highly specialized cells. Stem cells have variable proliferative properties and functions depending on their tissue compartment. Hematopoiesis is a continuous developmental process in which the hematopoietic stem cells (HSCs) produce the various blood lineages depending on specific cell fate variations [1]. The most primitive stem cells express the cell surface antigen CD34 and receptors for the early-acting hematopoietic growth factors: kinase domain receptor (KDR [flk-1]), vascular endothelial growth factor and the positive hematopoietic development regulators, c-kit and FLT-3 [2].

For the purpose of transplantation HSCs can be collected from bone marrow (BM) or peripheral blood. Hematopoietic reconstitution after BM ablation depends on the migration and "homing" of these intravenously transfused stem cells to the hematopoietic microenvironment in the BM niches of the recipient (Fig. 1). They form a small part of the transplant recipient's stem cell pool and divide slowly with limited expansion and reverting to a dormant state when mature compartments are fully reconstituted. However, despite adverse conditions in the host BM niches, the infused HSCs generate sufficient progenitors to repopulate the host hematopoietic system with mature cells (Fig. 2).

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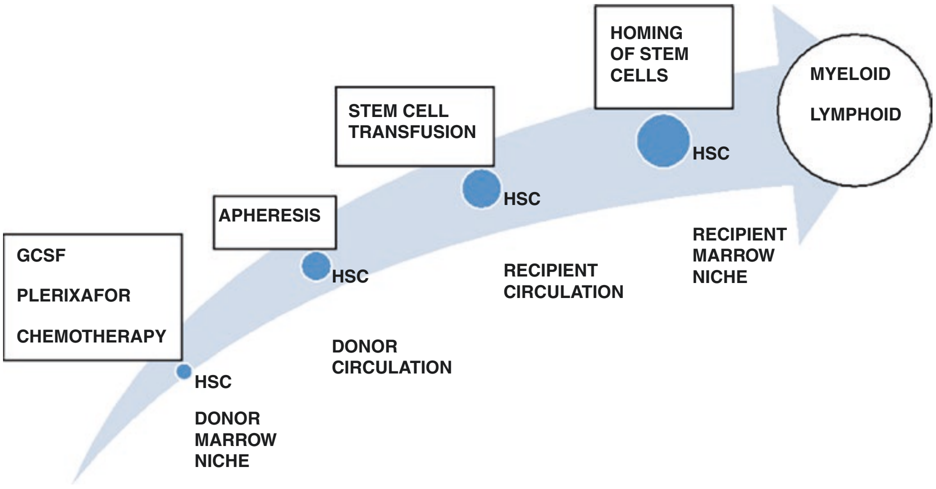
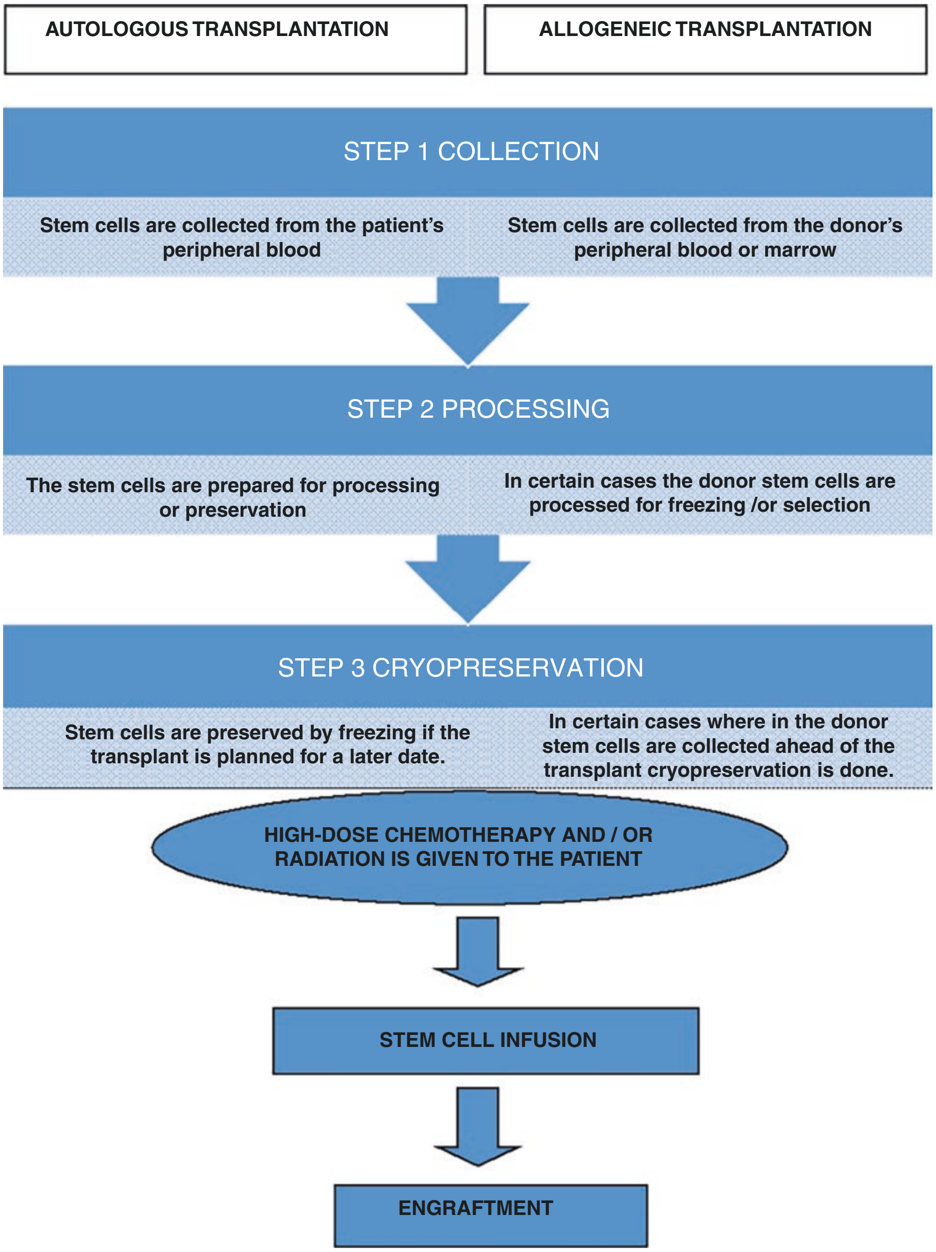

HOMING OF STEM CELLS
MYELOID
LYMPHOID
STEM CELL TRANSFUSION
HSC
HSC
APHERESIS
RECIPIENT MARROW NICHE
GCSF
PLERIXAFOR
CHEMOTHERAPY
HSC
RECIPIENT CIRCULATION
DONOR CIRCULATION
HSC
DONOR MARROW NICHE

Fig. 1 Homing of hematopoietic stem cells to the bone-marrow niches in transplant recipient


AUTOLOGOUS TRANSPLANTATION
ALLOGENEIC TRANSPLANTATION
STEP 1 COLLECTION
STEP 2 PROCESSING
STEP 3 CRYOPRESERVATION
HIGH-DOSE CHEMOTHERAPY AND / OR RADIATION IS GIVEN TO THE PATIENT
STEM CELL INFUSION
ENGRAFTMENT

Stem cells are collected from the patient's peripheral blood

Stem cells are collected from the donor's peripheral blood or marrow

The stem cells are prepared for processing or preservation

In certain cases the donor stem cells are processed for freezing /or selection

Stem cells are preserved by freezing if the transplant is planned for a later date.

In certain cases where in the donor stem cells are collected ahead of the transplant cryopreservation is done.

Fig. 2 Outline of hematopoietic stem cell transplantation

2 Historical Aspects

After 50 years of hematopoietic stem-cell transplantation for cancer therapy, it has progressed from several complications to becoming a standard treatment for many hematological malignancies.

The era of hematopoietic stem cell transplantation began during the first atomic bomb explosions, by Leon Jacobson et al. in 1949 who showed that mice could be protected from the lethal effects of ionizing radiation on bone marrow by shielding their spleens with lead [3]. Jacobson further demonstrated a similar protective effect by shielding the femur. Lorenz and colleagues showed that protection against radiation could also be conferred by intravenous infusions of bone marrow [4]. Initially, it was thought that protection was affected by some "hormone" or "growth factor" in the spleen or bone marrow that stimulated hematological recovery [3, 5]. In the 1950s, Barnes and Loutit [6] and Main and Prehn [7] have shown that radiation protection was due to transplanted stem cells [6–10].

The fact that all hematopoietic stem cells arise from pluripotent stem cells led to widespread research into the potential for bone-marrow transplantation as a treatment for hematological malignancies, involving intensive irradiation and intravenous infusion of bone-marrow cells to protect the recipient from life threatening bone-marrow aplasia. The early studies were pioneered by E. Donnall Thomas and colleagues who began their human bone-marrow grafting program in 1955, and showed in 1957 that human hematopoietic stem-cell transplants were, for the most part, unsuccessful, with only one patient undergoing a transient engraftment [10]. The other patients died of progressive disease or allograft failure. Despite the poor results, these trials showed for the first time that when grafts were carefully screened before infusion (to remove fat and bone particles), relatively large amounts of bone marrow could be administered to human patients without serious side effects. In 1959, three landmark papers were published that described the transplantation of bone marrow into leukemia patients and into victims of radiation exposure [11–13].

The second half of the 1960s saw the development of high-dose conditioning regimens. These consisted of the maximally tolerated doses of TBI and/or chemotherapy (such as the alkylating agent cyclophosphamide), which not only served to kill cancer cells, but also suppressed the hosts' immune systems so that graft rejection could be prevented.

In the latter half of the 1980s, technologies were refined and alternative graft donors and sources were found. T-cell depletion [14] and pharmaceutical agents [15] were shown to minimize graft versus host disease (GVHD). Due to the fact that only around 35% of patients have HLA-matched siblings, the use of alternative donors began to include extended family members who share one HLA haplotype, and to unrelated HLA-matched and -mismatched donors. Alternative sources of stem cells, such as cord blood and peripheral blood have begun to be employed as potential graft sources.

In order to overcome the hurdle of age, recently developed less intensive hematopoietic stem-cell transplantation programs with reduced intensity conditioning, rely less (or not at all) on chemoradiation therapy and shift the burden of tumor-cell killing toward graft versus tumor effects [16]. These so called nonmyeloablative or mini-transplant approaches, have been translated directly from preclinical models into the clinic.

3 Indications for Hematopoietic Stem Cell Transplant (Table 1)

Table 1 Indications for hematopoietic stem cell transplant

Autologous transplantation
Cancers
Multiple myeloma
Non-Hodgkin's lymphoma
Hodgkin's disease
Acute myeloid leukemia
Neuroblastoma
Germ-cell tumors
Ewing sarcoma
Other diseases
Autoimmune disorders
Amyloidosis
Allogeneic transplantation
Cancers
Acute myeloid leukemia
Acute lymphoblastic leukemia
Chronic myeloid leukemia
Myelodysplastic syndromes
Myeloproliferative disorders
Non-Hodgkin's lymphoma
Hodgkin's disease
Chronic lymphocytic leukemia
Multiple myeloma
Juvenile chronic myeloid leukemia
Other diseases
Aplastic anemia
Paroxysmal nocturnal hemoglobinuria
Fanconi anemia
Blackfan–Diamond anemia
Thalassemia major
Sickle cell anemia
Severe combined immunodeficiency
Wiskott–Aldrich syndrome
Inborn errors of metabolism

4 Types of Hematopoietic Stem Cell Transplantation

The types of hematopoietic stem cell transplantation are as follows:

- Autologous transplants
- Allogeneic transplants
  - **Related donor**
    - Matched sibling donor
    - Haploidentical donor
    - Umbilical cord
  - **Unrelated donor**
    - Matched-unrelated donor
    - Single antigen mismatched donor
    - Umbilical cord
- Syngeneic transplants

The advantages and disadvantages of the types of transplantation are presented in Table 2.

Table 2 Advantages and disadvantages of types of transplants

Type of transplant	Advantages	Disadvantages
Allogeneic		
Sibling donor 10/10 HLA match or 9/10 match	Rapid identification of match (2 weeks) Lower rate of graft rejection (2–5%)	GVHD (25–45%) in a non-T deplete marrow graft The probability of a match with siblings is only 30%
Matched-unrelated donor	Broadens the donor availability (60–70% will have a potential match) Greater graft vs. tumor effect and hence better chance of progression-free survival	Longer duration to find a match (2–6 months) Higher graft failure risk (5–10%) Higher risk of GVHD (50–60%) Higher risk of nonrelapse mortality
Umbilical cord donor	Lesser degree of match can be used Much lower rate of GVHD despite one and two antigens mismatch (10–20%)	Limited dose (difficulty for a large recipient) Delayed engraftment Higher chances of graft failure (10%) No possibility of DLI for posttransplant relapse
Haploidentical-related donor	Almost all patients have a sibling or parent or both who can be a potential donor	Profound immunosuppression Higher infectious complications Higher risk of graft failure (10–15%)
Syngeneic		
Identical twin	Immunosuppression not required No GVHD	No GVT effect

5 Biological Principles of High-Dose Chemotherapy and Radiation

High-dose chemotherapy is required to “condition” or “prepare” patients prior to a transplant for eradicating the tumor and “creating space,” so that graft would home and then reconstitute the host immune system and accordingly named as conditioning or preparative regimen. This was accomplished by applying an empiric combination of total body irradiation (TBI) and cyclophosphamide [17]. In the later years, combination chemotherapy without TBI began [18]. The concept of “creating space” has gradually been replaced by a more diverse and complex, mechanisms involved in engraftment. Also, the idea of eradicating tumor cells with high-dose chemotherapy and replacing the patient’s immune system with that of the donor has been substituted by engraftment along with tumor killing facilitated by the conditioning regimen. After engraftment of the immune cells, a **graft versus tumor effect** is exerted against residual tumor cells to accomplish long-term freedom from progression. A wide range of combinations of drugs with synergistic antitumor activity with minimal risk for normal tissue toxicity are increasingly employed now in conditioning. These allow to improve the antileukemic effects and the immunosuppressive capability of the preparative regimen. Further, treatment intensity can be modulated in proportion to the effectiveness of immune-mediated tumor killing by the graft [19–21]. These approaches aim at optimizing patient safety and minimizing serious treatment-related adverse events while maximizing antitumor effects. The more recent introduction of nucleoside analog (NA) combinations in pretransplant conditioning provides both the intense immunosuppression necessary to facilitate engraftment and an improved antitumor effect by inducing DNA damage and inhibiting DNA repair. The various drugs used in hematopoietic stem cell transplant are as follows:

- **Autologous transplants**
  - MEL
  - VP-16
  - BCNU
  - Ara-C
  - Cyclophosphamide
  - Busulfan
  - Carboplatin
  - MAb
  - ThioTEPA
  - TBI
  - Gemcitabine
  - Treosulfan
  - Bortezomib
  - CCNU

- **Allogeneic transplants**
    Fludarabine
    Cyclophosphamide
    Busulfan
    TBI
    ATG
    MEL
    MAb
    VP-16
    ThioTEPA
    Ara-C
    BCNU
    Treosulfan
    Clofarabine
    Pentostatin
    TLI/TNI/TAI

6 Total Body Irradiation

Irradiation is used primarily as a form of systemic therapy utilizing high-energy photons and large fields to deliver total body irradiation (TBI). In addition, total lymphoid irradiation (TLI) and locoregional irradiation directed to areas of higher tumor burden have also been combined with chemotherapy in HCT conditioning regimens. A primary role of TBI is the eradication of malignant cells; however, it also provides a powerful means of immunosuppression to prevent graft rejection. TBI is often combined with chemotherapy in conditioning regimens and offers distinct advantages over chemotherapy. Unlike chemotherapy, delivery of radiation therapy to the tumor site is not dependent on blood supply or influenced by interpatient variability of drug absorption, metabolism, biodistribution, or clearance kinetics. Radiation therapy can reach potential sanctuary sites, such as the testes and central nervous system. Chemotherapy-resistant clones may still be sensitive to irradiation. Unlike in chemotherapy, the radiation dose can be preferentially distributed to areas of greatest tumor burden and restricted to critical normal organs. Typical TBI schedules deliver a total dose of 10 to 14 Gy at 1.2 Gy three times daily (TID), 2 Gy twice daily (BID) or 3 Gy once daily (QD). A variety of TBI schedules have been evaluated to reduce toxicities and improve relapse rates and the therapeutic index. Factors that are of radiobiologic importance include total dose, fraction schedule, fraction size, use of organ shielding and dose rate. The long-term complications of TBI include Endocrine and reproductive (gonadal) insufficiency, growth disorders (in childhood), hypothyroidism, lung fibrosis, cataract, secondary malignancies, irreversible alopecia, cardiomyopathy.

Indications for TBI are as follows:

Leukemias in adults and childhood:
- Acute lymphoblastic leukemia (ALL)
- Acute myeloid leukemia (AML)
- Chronic myeloid leukemia (CML)
- Myelodysplastic syndrome (MDS)

Optional indications
- Solid tumors in childhood:
    - Neuroblastomas
    - Ewing sarcomas
    - Plasmocytomas/multiple myelomas

7 Outcomes of HSCT (in Adults) in Various Diseases (Table 3)

Table 3 Outcomes of HSCT (in adults) in various diseases

Disease status	Role of HSCT
AML	HSCT is used as consolidation strategy in first CR for certain risk groups, for patients who are refractory to standard chemotherapy and at relapse. Allogeneic HSCT is not recommended for patients in first CR with good risk AML. However, in patients with acute promyelocytic leukemia not achieving a molecular response after frontline consolidation or after salvage treatment, an allogeneic HSCT is recommended. Patients in first CR with intermediate-risk and high-risk AML are candidates for HLA-identical sibling donor HSCT.
ALL	Adults with ALL with poor prognostic features, for example, t(9;22) or t(4;11), or failure of induction chemotherapy, are candidates for allogeneic HSCT from either an HLA-identical sibling or an unrelated donor. Patients with relapse are candidates for allogeneic HSCT from an HLA-identical sibling, an unrelated donor or other alternative donors such as cord blood or haploidentical donor.
MDS	Allogeneic HSCT is considered the treatment of choice for adult patients with myelodysplastic syndrome (MDS) or AML evolved from MDS and offers a good chance of long-term disease-free survival. Whether the transplant is done upfront or after a few initial courses of hypomethylating therapy depends on the baseline blast count. A pretransplant blast count of less than 5% is beneficial.
CML	HSCT remains the only curative treatment for CML. However with the advent of TKI therapy, the indications are few. Patients in the blast crisis at diagnosis should be referred for HSCT as soon as possible. While preparing for HSCT, initial therapy with TKI or intensive therapy ± TKI might be an option. HSCT should be performed as soon as possible after achieving the second chronic phase. Patients with ABL mutations that are resistant to the second-generation TKI may benefit from HCT.
NHL	Autologous HSCT is the standard therapy for patients with chemosensitive relapse of diffuse large B-cell lymphoma (DLBCL) [22]. Patients with refractory disease, early relapse—within 12 months, have a very poor prognosis. The role of CART cell therapy and bispecifics becomes important here.
Myeloma	Autologous HSCT is the standard of care for all the eligible patients who respond to first-line treatment. Age should be considered in light with the patient's general health and fitness. Tandem autologous HSCTs have been shown to be superior to one autologous HSCT, although the benefit of the second transplant seems to be restricted to patients not achieving CR or very good PR with the first transplant.
Hodgkin lymphoma	Autologous HSCT is the standard therapy for patients with Hodgkin's lymphoma (HL) in first chemosensitive relapse [23]. Refractory disease if responds to salvage therapy (chemotherapy, immunotherapy and brentuximab or a combination of these) might benefit from an autologous HSCT [24, 25]. Allogeneic HSCT has mainly been used as salvage therapy for multiply relapsed or refractory HL patients.

8 Outcomes of HSCT (in Children) in Various Diseases (Table 4)

Table 4 Outcomes of HSCT (in children) in various diseases

Disease status	Role of HSCT
AML	In pediatric AML, the role of allo-HSCT in CR1 remains for the high risk. Infant AML and children with FAB M0, M6 or M7 AML are indications for allogeneic HSCT. In children with relapsed AML, allogeneic HSCT is indicated either from a sibling or an unrelated donor.
ALL	The indication for HSCT in children with ALL in CR1 is limited to the subpopulation of the high-risk ALL with an estimated EFS of <50% especially groups like persistent minimal residual disease. ALL patients, who experience an early marrow relapse, are candidates for transplant with sibling or alternative donors as the outcomes are similar.
MDS	Allogeneic HSCT from a sibling donor or a well-matched-unrelated donor is the treatment of choice for children with primary MDS, including juvenile myelomonocytic leukemia and secondary AML.
Lymphomas	Patients who fail to respond to upfront therapy or those with chemo-sensitive relapsed diseases can achieve long-term disease-free survival after autologous HSCT. Allogeneic HSCT is beneficial in multiply relapsed refractory setting.
Solid tumors	Neuroblastoma (stage IV beyond the age of 1 year, or high-risk factors in lower stages) is still the only indication for which the benefit of high-dose therapy with autologous HSCT has been shown by randomized trials [26, 27]. Children and adolescents with solid tumors might undergo autologous HSCT after high-dose chemotherapy within clinical research trials, in the following situations: • Neuroblastoma (high risk, >CR1) • Ewing's sarcoma (high risk or >CR1) • Brain tumors: children with medulloblastoma and high-grade gliomas responsive to chemotherapy in an attempt to avoid or postpone radiotherapy. • Germ cell tumors: after a relapse or with progressive/refractory disease

9 Current Status of HSCT: Indian Perspective

The first bone-marrow transplantation in India was done in 1983 at Tata Memorial Hospital, Mumbai. There has been a steady rise in number of transplant centers in India over last few years. In India, the larger transplant centers are: Tata Memorial Hospital, Mumbai; Christian Medical College, Vellore; AIIMS, New Delhi; Apollo Cancer Hospital, Chennai; Army Hospital R&R, New Delhi; SGPGI, Lucknow; Cancer Institute (WIA), Chennai; Rajiv Gandhi Cancer Institute, New Delhi; PGIMER, Chandigarh. The average cost varies from Rs 6 to 15 lakhs per procedure depending on the type of transplant and the center.

Indian Stem Cell Transplant Registry (ISCTR) (Nov 2017) data reveal a definite increase in the total number of transplant centers reporting from 52 to 65, and total number of transplants also continue to increase by around 10% per year with 2016 seeing 1878 transplants reported to ISCTR.

Infections especially early bacterial infections are the major threat to success of any transplant program. Sixty-five transplant centers from 25 countries across Europe, Australia and Asia reported data on 655 GNR episodes and 704 pathogens in 591 patients. Unfortunately, half of these gram-negative bacteria were fluoroquinolone and non-carbapenem-resistant; 18.5% carbapenem-resistant and 35.2% multidrug-resistant [28]. Interestingly, total resistance rates were similar in community-acquired infections. Gram negative sepsis has been major cause of mortality and morbidity in India. Kamble et al. [29] reported data on 516 blood culture samples received from 74 patients from different sites. Sixty-three cultures were positive in 21 patients (12%). There is an urgent need to curb the emergence of MDR organisms in our country.

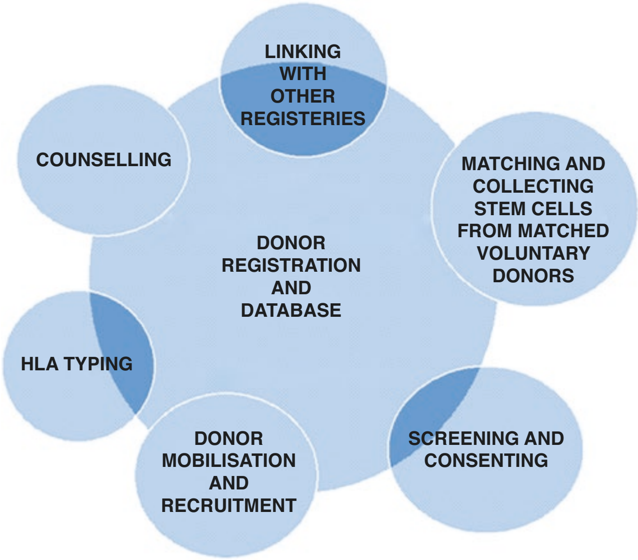

LINKING WITH OTHER REGISTERIES
COUNSELLING
MATCHING AND COLLECTING STEM CELLS FROM MATCHED VOLUNTARY DONORS
DONOR REGISTRATION AND DATABASE
HLA TYPING
DONOR MOBILISATION AND RECRUITMENT
SCREENING AND CONSENTING

Fig. 3 Activities in a marrow donor registry program

Unrelated donor registries in India include DATRI and MDRI (marrow donor registry of India) (Fig. 3).

The MDRI is India's first NGO that maintains a computerized database of voluntary, unrelated stem cell donors and facilitates blood stem cell transplants for patients with life-threatening blood diseases. It recruits donors, maintains a registry of volunteer potential donors and initiates a search for HLA typed stem cell donors for a patient requiring a transplant anywhere across globe. This was the noble initiative of a Mumbai-based hematologist, Dr. Sunil Parekh, in 2008.

DATRI is another Indian marrow donor registry that was cofounded and run by Raghu Rajagopal, an entrepreneur in Chennai. The registry has partnered with a US high-resolution tissue-typing company called HistoGenetics, which has provided DATRI with financial support and carries out HLA typing for potential donors.

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Part IV

Solid Tumors

Central Nervous System (CNS) Tumors

Aliasgar Moiyadi, Vikas Singh, Raees Tonse,
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Abbreviations

ATRT	Atypical teratoid/rhabdoid tumors
BBB	Blood–brain barrier
CNS	Central nervous system
CT	Computed tomography
DTI	Diffusion tractography imaging
EGFR	Epidermal growth factor receptor
ETMR	Embryonal tumor with multi-layered rosettes
GCT	Germ cell tumor
GTCS	Generalized tonic-clonic convulsion
IDH	Isocitrate dehydrogenase
IGRT	Image-guided radiation therapy
IMRT	Intensity-modulated radiation therapy
MB	Medulloblastoma
MRI	Magnetic resonance imaging
MRS	MR spectroscopy
PCNSL	Primary central nervous system lymphoma
PCV	Procarbazine, lomustine, and vincristine
PET	Positron emission tomography
PNET	Primitive neuro-ectodermal tumor
PT	Proton beam radiation therapy
PXA	Pleomorphic xanthoastrocytoma
SRS	Stereotactic radiosurgery SVZ sub-ventricular zone
VMAT	Volumetric modulated arc therapy
WBRT	Whole brain radiation therapy

1 Introduction

Central nervous system (CNS) tumors include a wide spectrum of tumors that vary with regard to age, location, histology, and clinical outcomes. Epidemiologic studies have shown a trend toward increasing incidence of brain tumors attributable to increased life expectancy, improved detection rates (with better and advanced imaging techniques), and more systematic documentation and reporting due to the introduction of cancer registries. The delicate and exquisitely eloquent nature of the brain and spinal cord poses a significant dilemma in treating these tumors (where oncological principles of radicality must be counter balanced against the need for function preservation). Recent advances in diagnostic imaging, intraoperative surgical adjuncts, radiotherapy techniques, and the introduction of newer systemic therapies have helped improve patient outcomes. Nonetheless optimizing treatment outcomes remains an ongoing challenge and area of intense research.

2 Epidemiology (Global and Indian Perspectives)

CNS tumors constitute approximately 2% of all malignancies. Though primary brain tumors account for about 2.8% of all cancer deaths, their adverse impact is disproportionately higher, in terms of years of life lost from cancer [1]. Brain tumors represent approximately 85–90% of all CNS tumors, of which, the age-adjusted average annual incidence rates vary among the population. In general, the incidence in males is more than in females. Glioma and meningioma are common primary tumors (age-adjusted average annual incidence rates of 6.45 and 5.55 per 100,000 population, respectively) [2]. The incidence of gliomas, germ cell tumors, and cysts is higher in men, whereas women have a higher incidence of meningioma. Spinal tumors account for 10–15% of

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primary CNS tumors [3]. Most primary CNS spinal tumors are benign (in contrast to intracranial tumors) and are likely to have compressive rather than invasive features [4].

Brain metastases are the commonest brain tumors seen in adults (much less common in children), comprising over half of all brain tumors overall. Depending on the level of screening and general outcomes of other primary cancers in the region, the incidence of metastases can vary. Fifteen to thirty percent of patients with cancer develop cerebral metastasis [5]. The most common site of primary is the lung, breast, melanoma, colon, and kidney. Melanomas have the highest propensity for developing cerebral metastasis followed by lung and breast carcinomas. Up to 10–15% of cerebral metastases may yield no known primary in spite of extensive workup [6].

Brain tumors are the second most common form of malignancy (after leukemia) and a leading cause of cancer-related death in children. CNS tumors in children (0–18 years) differ from those of adults, particularly with regard to their location and histologic/molecular subtypes [7]; medulloblastomas and astrocytomas are more commonly encountered than other histologic subtypes. In children, the majority (70%) of tumors are infratentorial as compared to only 30% in adults. They are also responsible for 20% of malignant tumors diagnosed before the age of 15 [8].

Data from the Indian subcontinent are sparse due to a lack of cancer registries, and most published literature is institution based [9, 10]. Incidence of CNS tumors in India ranges from 5 to 10 per 100,000 population, and there has been an increasing trend in registrations at referral centers. At our own center, we have seen an exponential rise in registered cases over the last decade, the dip during the pandemic period (2020–21) notwithstanding (Fig. 1). In adults, the most common brain primary tumors are astrocytomas (38.7%) High-grade glioma (59.5%) is the most frequently diagnosed histologic sub type amongst astrocytomas. The median age of diagnosis of glial tumors was seen to be at least a decade earlier than reported in the Western population, which may be due to the lower life expectancy and a higher proportion of the young population in India [11]. Institutional studies report similar histological distribution of tumor types in adults as well as children as is the global trend [10, 12].

From an etiologic perspective, the heterogeneity of histologic diagnoses within CNS tumors indicates multiple probable causative mechanisms. CNS tumor incidence varies among different populations with certain ethnic groups like Jews having a higher propensity [13, 14]. Environmental factors may contribute to the increased incidence of tumors in certain regions [15, 16]. Multiple factors like medical history (and immunologic status), family history, and genetic factors have been reported to have a weak and inconsistent association with the risk of CNS tumor development. Host factors like rare genetic syndromes, a family history of CNS tumors, and congenital malformations are known to have the strongest association with the development of CNS tumors. Certain hereditary and congenital diseases with increased risk of CNS tumors [17] are neurofibromatosis [18], Tuberous scelorosis, Li–Fraumeni tumor syndrome [19], ataxia telangiectasia [20], Gorlin syndrome, and Turcot syndrome [21]. The loss of tumor suppressor genes like p53 seems to be a fundamental mechanism in the development of several CNS tumor types [22, 23]. Cytogenetic abnormalities like the loss/translocation of parts of chromosome 22 in familial meningioma and acoustic neuroma and gains on chromosome 7/loss on 9 in gliomas have been described [24–27].

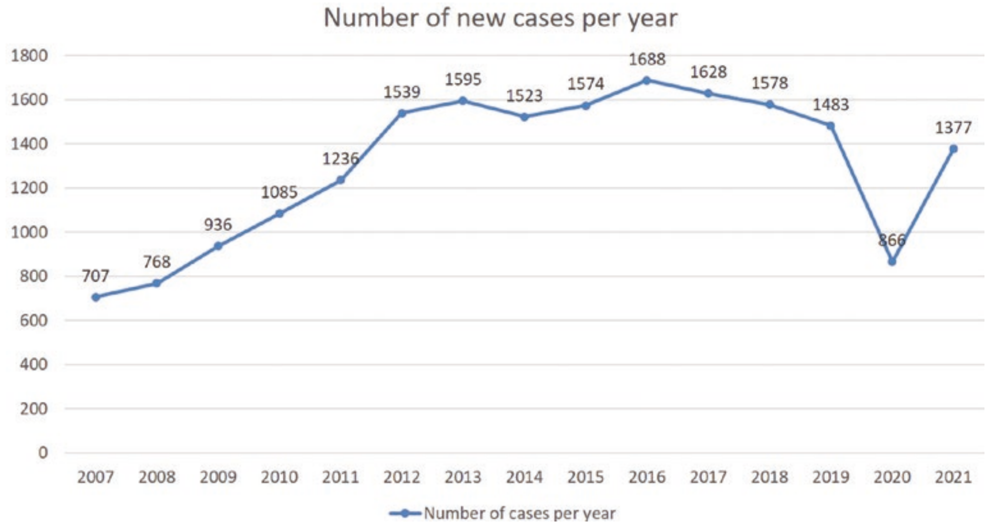


Fig. 1 Number of new case registrations in neuro-oncology, Tata Memorial Centre 2007–2017

A causal relationship between ionizing radiation and CNS tumors is well known. Published literature has shown that exposures in utero [28, 29], high-dose irradiation in childhood [30] and in adult life [31] increase the risk of CNS tumor. A possible association between mobile (cellular) telephone use and CNS tumor risk remains highly debatable. However, extensive research on the association between mobile phone usage and CNS tumor development has not shown a substantially increased risk [32, 33]. Associations between diet, occupation, smoking, and immunocompromised states and CNS tumors in humans have been postulated but remain weak and inconsistent [34–37]. As the etiology of CNS tumors remains poorly understood, more multicenter prospective studies in the future would help to achieve better consensus on the causal associations of brain tumor.

3 Clinical Presentation

Clinical presentation in a patient with CNS malignancy can be varied depending on the age, location of the tumor, size, and rate of growth. Tumors produce symptoms either by compression or infiltration of functioning nervous tissue. Mass effect due to increasing tumor bulk may lead to local (compressive symptoms) or symptoms due to raised intracranial pressure (ICP).

Neurologic deficit is seen in almost two-thirds of all brain tumors [38] and is usually progressive, though sudden acute neurological worsening may be associated with tumoral bleeds. Symptoms depend on the location of the tumor varying from subtle cognitive defects (like inability to perform routine tasks, emotional lability, forgetfulness, reduction in the range of mental activity, indifference to social practices, and behavioral changes) to more obvious "hard" neurological deficits like motor and speech defects. Figure 2 shows common symptoms associated with different locations of tumors.

Headache with/without vomiting can be the presenting symptom in 54% of the patients [39]. It may be associated with or without raised intracranial pressure (ICP), the latter being due to invasion or compression of pain-sensitive structures like dura, blood vessels, or periosteum.

Common symptoms suggesting raised ICP are headache, vomiting, diminution of vision, excessive somnolence, and new onset focal neurological deficits. Classic early morning headache described in the literature is seen infrequently.

Seizures may be seen in 26% of patients as a presenting symptom. Often, they are focal at onset (a function of cortical irritation due to the tumor) but may spread secondarily resulting in a generalized tonic-clonic convulsion (GTCS).

Tumors in sella/suprasellar location (pituitary adenoma, craniopharyngioma, etc.) would typically present with worsening visual field deficits due to compression of the optic chiasma. A secretory pituitary tumor would have manifestations of excessive hormone production like cushingoid features (cortisol excess), acromegaly (growth hormone excess), or very rarely hyperthyroidism. A large non-functioning sellar/suprasellar mass can also present with features of hypopituitarism due to compression of the pituitary gland.

Tumors in the cerebello-pontine angle location have a characteristic sensori-neural type of hearing loss due to the involvement of vestibulo-cochlear nerve. There may be associated imbalance while walking, tinnitus, headaches, and facial nerve weakness with increasing tumor size due to local mass effect.

Intraventricular location, frontal and occipital poles are considered to be silent zones of the brain, and tumors at these locations do not manifest until they are very large, often only showing raised ICP features.

Signs and symptoms in spinal tumors depend upon the location (cervical, dorsal, lumbar, or sacral) or plane (extradural, intradural extra medullary, or intramedullary).

- Pain is the most common complaint. Radicular pain that increases with Valsalva and spine movement in a location uncommon for intervertebral disc disease should raise suspicion of a spinal cord tumor. Pain during recumbency ("nocturnal pain") is classic for spinal cord tumors.
- Motor disturbances. Quadriparesis (in cervical cord tumors) or paraperesis (in dorso-lumbar tumors) are frequent manifestations of intradural tumors.
- Syringomyelic syndrome. Syringomyelic syndrome suggests intra-medullary spinal cord tumors with syringomyelia. This includes lower motor neuron features (segmental weakness with loss of reflexes and muscle atrophy) in the upper limb and upper motor neuron features (increased tone, exaggerated reflexes) in the lower limbs.
- Dissociated sensory loss. Decreased pain and temperature with preserved light touch can be seen in intramedullary spinal cord tumors.
- Sphincter disturbances. Sphincter disturbances are sometimes seen and usually urogenital (anal less common) in nature, viz. hesitancy, retention, and incontinence. They may be early signs in conus/cauda equina lesions.

In all patients, a detailed neurological examination usually provides a clue to the diagnosis and is essential as a baseline examination during follow-up. Irrespective of the symptoms, a detailed neurological examination (and in brain tumors, a detailed neuropsychological evaluation) should be performed for all cases.

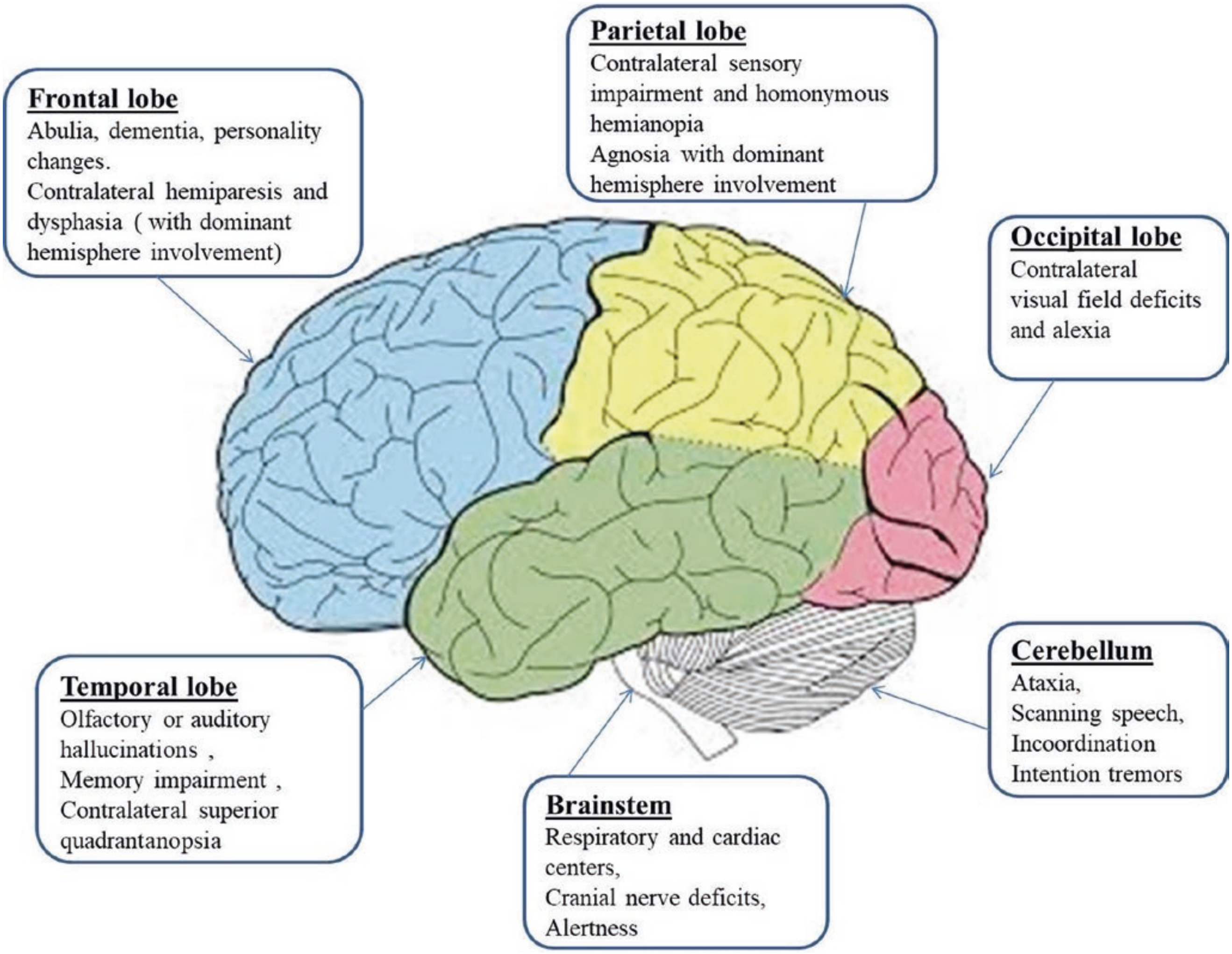

Frontal lobe
Abulia, dementia, personality changes.
Contralateral hemiparesis and dysphasia (with dominant hemisphere involvement)
Parietal lobe
Contralateral sensory impairment and homonymous hemianopia
Agnosia with dominant hemisphere involvement
Occipital lobe
Contralateral visual field deficits and alexia
Temporal lobe
Olfactory or auditory hallucinations ,
Memory impairment ,
Contralateral superior quadrantanopsia
Brainstem
Respiratory and cardiac centers,
Cranial nerve deficits,
Alertness
Cerebellum
Ataxia,
Scanning speech,
Incoordination
Intention tremors

Fig. 2 Common symptoms associated with different locations of tumors

4 Diagnostic Imaging and Work up

Several modalities may be used to aid in the diagnosis of primary and recurrent CNS tumors and assess the burden of the disease in cases with metastatic spread in the CNS. Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used imaging modalities. Although these modalities continue to evolve, advanced imaging techniques such as MR spectroscopy (MRS), diffusion-weighted MRI, CT and MR perfusion imaging, and bioimaging techniques like positron emission tomography (PET) are used routinely in clinical practice today for differentiating neoplastic disease from non-neoplastic ones. Functional MRI and diffusion tractography imaging (DTI) helps in intraoperative planning surgery in eloquent brain areas. These modalities also provide valuable information about the configuration of the lesion, vascularity, and tissue characteristics and relation to important surrounding neuro-vasculature Emerging research in texture analysis has spawned a new and exciting field of radiomics that has the potential to provide more detailed (including biological) information about tumors [40]. Thus, these investigations when used appropriately add significant information to the evaluation of patients with cerebral neoplasms.

CT brain with contrast is often the first screening tool for investigating a patient with suspected CNS neoplasm. Calcifications and bleed within the tumor can be particularly better assessed on a CT scan. CT angiography is sometimes used to assess the arterial supply and venous drainage of the tumors.

MRI is the gold standard for the evaluation of both brain and spine tumors. It provides reliable information on the probable histologic type and grade of the malignancy along with precise anatomical localization. A minimum mandatory

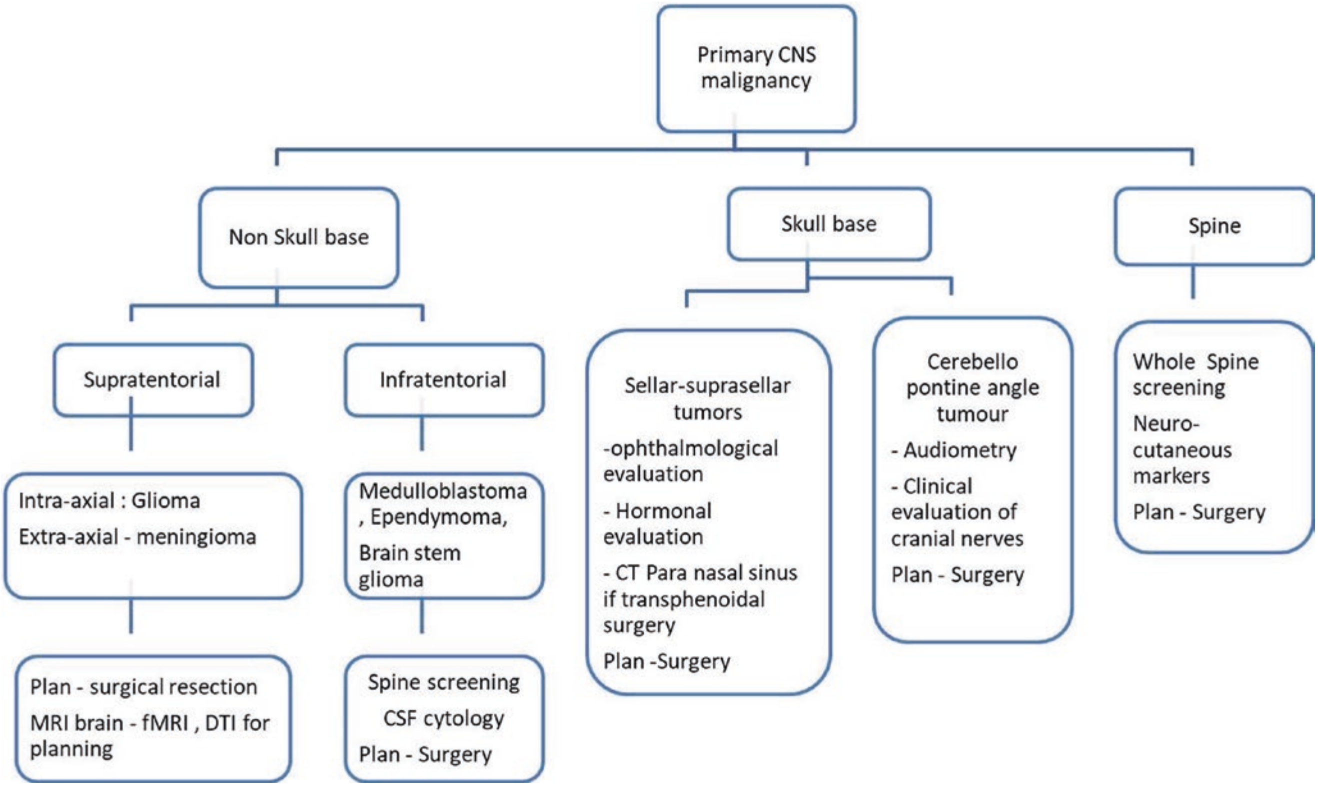

Primary CNS malignancy
Non Skull base
Skull base
Spine
Supratentorial
Infratentorial
Intra-axial : Glioma
Extra-axial - meningioma
Medulloblastoma , Ependymoma,
Brain stem glioma
Plan - surgical resection
MRI brain - fMRI , DTI for planning
Spine screening
CSF cytology
Plan - Surgery
Sellar-suprasellar tumors
-ophthalmological evaluation
- Hormonal evaluation
- CT Para nasal sinus if transphenoidal surgery
Plan -Surgery
Cerebello pontine angle tumour
- Audiometry
- Clinical evaluation of cranial nerves
Plan - Surgery
Whole Spine screening
Neuro-cutaneous markers
Plan - Surgery

Fig. 3 Algorithm showing the diagnostic evaluation plan for a suspected CNS tumor

brain tumor MR protocol should include routine sequences as well as MR spectroscopy and MR perfusion. fMRI is particularly performed in patients with lesion adjacent to eloquent cortex to define its relation to tumor, especially when awake surgery has been planned. DTI helps to assess the proximity of the tumor to the deep white matter tracts. Both of these can be used intra-operatively to facilitate and tailor surgical resections (image-guided surgery).

4.1 Additional Investigations and Work-Up

In selected cases, additional workup may be required to aid diagnosis and stage tumors. Figure 3 shows a diagnostic evaluation plan for common CNS tumors.

CSF analysis for malignant cells is done to rule out leptomeningeal spread of the disease particularly in fourth ventricular and pineal mass lesions. CSF and serum estimation of tumor markers (alfa fetoprotein, LDH, beta-HCG) should be performed in suspected cases of germ cell tumors. In a patient with suspected sellar/suprasellar mass lesion (like pituitary adenoma, craniopharyngioma), ophthalmological evaluation (visual fields, visual acuity) and endocrinological evaluation (blood hormones) should be performed.

5 Pathology of CNS Tumors and Tissue Diagnosis

CNS tumors comprise a wide spectrum of pathologies, and tissue diagnosis is imperative for the institution of appropriate multimodal therapy. The 2021 WHO classification has led to a paradigm shift in the classification of CNS tumors emphasizing an integrated diagnosis comprising basic histo-morphology along with molecular characterization, the latter forming a crucial part of the overall diagnosis [41]. This has resulted in the reorganization of many histological entities and regrouping of tumor types and subtypes with distinct molecular signatures, reflecting biological behavior and having a direct impact on therapeutic strategies as outlined below. Tissue diagnosis, therefore, is a vital part of the overall management of CNS tumors. Unlike other solid tumors, diagnosis is usually achieved during surgical resection itself as a one-stage procedure (except in unresectable locations where only a surgical biopsy is performed, either open or stereotactically using mage guidance). The risk of surgical biopsy in critical locations is always weighed against the added benefit of tissue diagnosis over the radiological diagnosis. Rarely (as in diffuse pontine gliomas) is non-surgical therapy initiated without a tissue diagnosis, based only on radiological characterization.

6 Surgical Management

Surgery is usually the first modality of treatment in virtually all CNS tumors. In some benign tumors, it may be the only treatment required. The principles of surgery remain more or less the same for all tumor types (with differences in approaches and strategies depending on the location and occasionally the biological nature of the tumors).

Surgery serves the following roles:

1. Maximal safe resection (whenever possible) of the tumor without incurring fresh neurologic deficits is the primary goal of surgery. Due to the unique location of these tumors, it is often not possible to resect them radically (as in other oncological surgeries) and the underlying tenet always remains "safe maximal resection."
2. Tissue diagnosis (in unresectable tumors/suspected non-glial/non-neoplastic etiologies) can be achieved, so as to guide further adjuvant treatment.
3. Relieves compressive symptoms, which is a major indication of cytoreductive surgery and can often be life-saving.
4. Surgery also provides an opportunity to deliver novel local therapies (many of which are currently experimental).
5. Cytoreductive surgery also facilitates subsequent adjuvant therapies by reducing the tumor burden and eliminating the hypoxic (therapy-resistant) core tumor mass.

The general principles of neuro-oncological surgery are as follows:

1. Meticulous pre-surgical evaluation is mandatory and usually comprises of a thorough evaluation of pre-operative neurologic status, adequate imaging studies, counseling of the patient and family about the nature of the disease and possible need for adjuvant treatment, and taking informed consent.
2. The brain and spinal cord are eloquent areas, and this limits radical resection in neuro-oncological practice. Deciding the safest operative corridor for an individual patient is of paramount importance as the rigid bony skull often limits adequate exposure required for surgical excision maximizing the tumor resection with preservation of neurologic function is critical. Many adjuncts are used intraoperatively to achieve these goals.
3. Some patients seen in an emergency setting (intraventricular mass lesions) with obstructive hydrocephalus would warrant a CSF diversionary procedure like endoscopic third ventriculostomy or ventriculo-peritoneal shunt.
4. Post-operative care and rehabilitation. Post-operative imaging (MRI preferably) should be performed within 72 h of the surgery. Intensive monitoring in an ICU for the development of fresh neurologic deficits/neurologic worsening or metabolic abnormalities and providing prompt treatment is of utmost importance. Occasionally surgical procedures may result in significant morbidity. Intense rehabilitation measures instituted promptly help in the improvement of overall quality of life (QOL) and help consolidate further adjuvant treatment.

6.1 Adjuncts in Neuro-oncological Surgery

Many adjuncts have been used routinely in neurosurgical practice to achieve this goal of maximal safe resection, such as:

1. Microscope. It has been routinely used in neurosurgical procedures. It provides improved illumination, magnification, and stereoscopic view at depth thus facilitating more radical and complex surgeries safely.
2. Intra-operative navigation. Intra-operative navigation systems are based on pre-operative imaging and help to plan the incision, localize the tumor intra-operatively and assess completeness of the resection. However, due to technical limitations (brain shift), the role in guiding resections is usually limited.
3. Intraoperative imaging. This allows real-time updates and guides resection control overcoming the limitations of navigation. IOMR is the gold standard but remains a logistical challenge at most centers [42]. IOUS is a useful, cost-effective alternative [43]. Our own experience with navigating the US has been very encouraging [44, 45]. Optical imaging techniques like the use of fluorescence (5-aminolevulinic acid) administered before surgery help to guide and maximize tumor resections, especially in high-grade gliomas [46].
4. Intra-operative neuro-monitoring: It helps to identify eloquent areas (motor strip), cranial nerves, and white matter tracts (corticospinal tracts) intra-operatively and allows

prediction and prevention of neural injury. There has been a progressive increase in the published literature supporting the role of neuro-monitoring for maximal safe resection [47]. Awake mapping allows the mapping of many other language and cognitive functions permitting radical resections in eloquent regions.

5. Endoscopy. Endoscopic techniques have been frequently used as a minimally invasive tool for the resection of brain tumors, especially skull base tumors, pituitary adenomas, craniopharyngiomas, and intraventricular tumors.
6. Local surgical therapies. Various local surgical therapies have been developed, and many more are under development for treating malignant brain tumors. Some of these include Carmustine wafer (Gliadel wafers), nanotherm therapy, and laser interstitial thermal therapy (LITT), especially in recurrent glioblastomas.

7 Adjuvant Treatment for Brain Tumors

Adjuvant therapy is often used after surgery, to minimize the risk of recurrences and improve disease control. It includes radiation therapy (RT), chemotherapy, and targeted therapy usually given to target the residual tumor or microscopic disease post-surgery. Radiation therapy (RT) forms a very integral component in the multi-modal management of many CNS tumors. Over the last few years, modern techniques of radiotherapy like intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), volumetric-modulated arc therapy (VMAT), stereotactic radiotherapy (SRT), and particle therapy like proton beam therapy have been increasingly used to minimize the irradiation to the normal brain without compromising dose essential for tumor control [48].

7.1 Radiotherapy Techniques

Linear accelerators are being commonly used which has the advantages of higher energy photons as compared to telecobalt machines. The incorporation of beam modifications like multi-leaf collimators in linear accelerators can treat complex irregularly shaped tumors. These have helped in moving from two-dimensional to three-dimensional conformal radiotherapy (3DCRT) techniques by properly directing radiation beams from various directions. Further improvements had been possible by variation of beam intensities which is known as intensity-modulated radiotherapy (IMRT) or using image guidance (IGRT) to increase treatment accuracy.

Proton beam radiation therapy (PT) allows dose reduction to normal tissues by allowing for more precise dose delivery due to the unique physical properties of protons known as a Bragg peak. This property permits tissue penetration to a variable depth, depending upon their energy, and deposit energy only at that depth in the tissue [49]. Protons have been shown to have unique and distinct advantages in terms of dose escalation, preservation of intelligence, and endocrine functions particularly in childhood and low-grade/benign tumors, reducing the incidence of second cancers because of lower integral dose and in cases of re-irradiation [50–52].

7.2 Systemic Therapy/Chemotherapy

Chemotherapy is used in neuro-oncology to augment the effect of radiotherapy, radio-sensitization, or for treatment of microscopic “out-of-field” tumor based on the principle of spatial cooperation. The intact blood–brain barrier (BBB) prevents access to the brain for several compounds and therefore achieving therapeutic concentrations remains an enormous challenge. Recent focus is on the generation of newer and effective systemic therapies, targeted agents, and immunotherapy agents for CNS tumors and many trials are currently ongoing [53]. Hereafter specific systemic therapies will be discussed with respect to the common tumor classes treated.

8 Management of Individual Tumor Types

This section will provide an overview of management principles for the commonly encountered tumor types. Whereas the WHO 2021 classification includes an exhaustive list of tumor types, treatment strategies for the more common tumors can be broadly grouped, and Figs. 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15 show the management pathways for these tumors followed at our center.

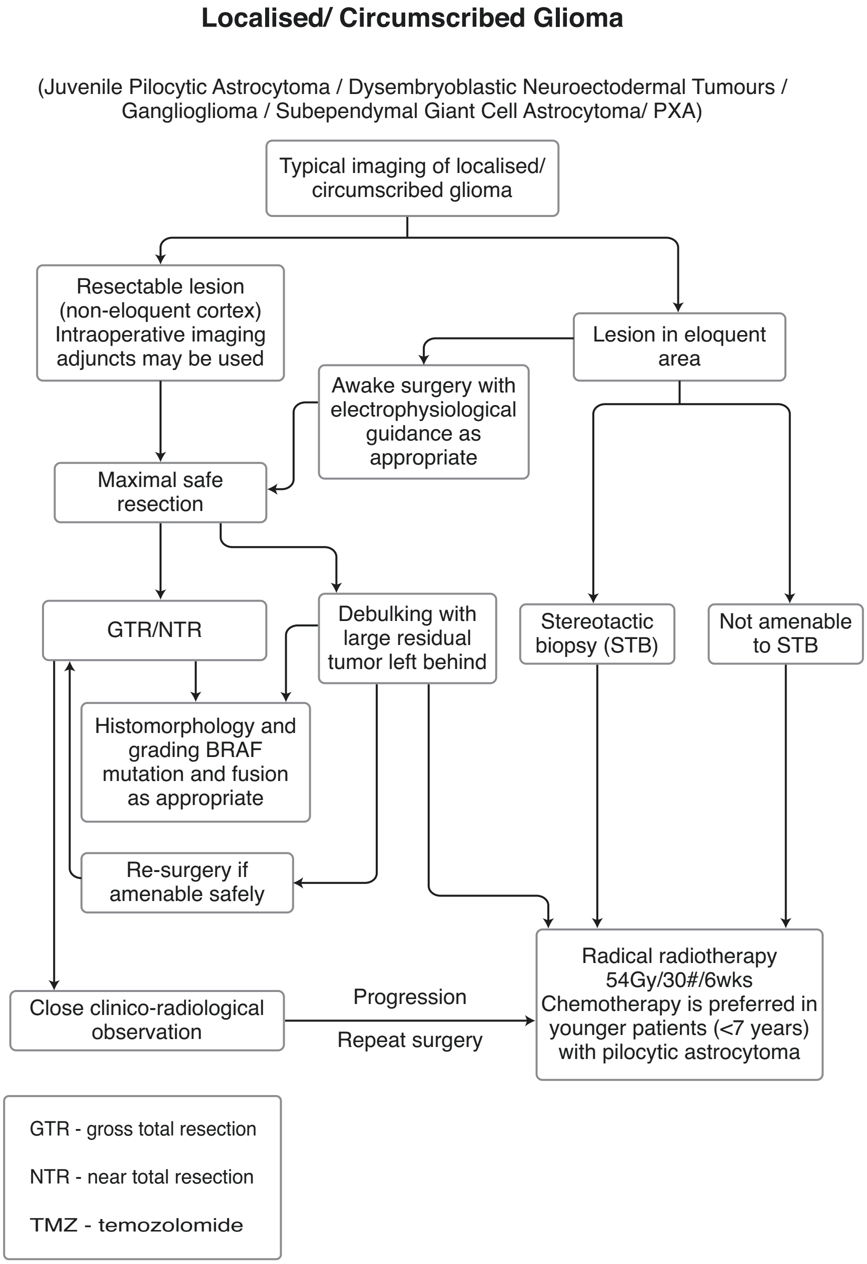
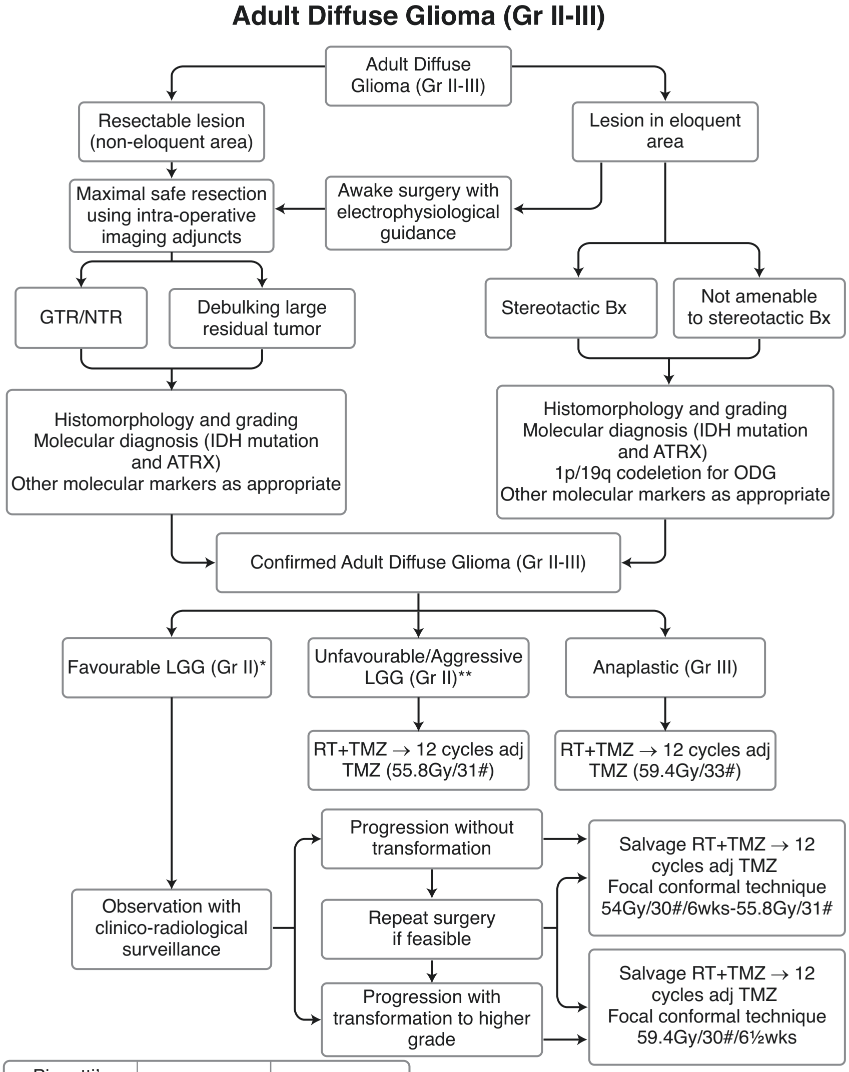

Localised/ Circumscribed Glioma
(Juvenile Pilocytic Astrocytoma / Dysembryoblastic Neuroectodermal Tumours / Ganglioglioma / Subependymal Giant Cell Astrocytoma/ PXA)
Typical imaging of localised/ circumscribed glioma
Resectable lesion (non-eloquent cortex) Intraoperative imaging adjuncts may be used
Lesion in eloquent area
Awake surgery with electrophysiological guidance as appropriate
Maximal safe resection
GTR/NTR
Debulking with large residual tumor left behind
Stereotactic biopsy (STB)
Not amenable to STB
Histomorphology and grading BRAF mutation and fusion as appropriate
Re-surgery if amenable safely
Radical radiotherapy 54Gy/30#/6wks Chemotherapy is preferred in younger patients (<7 years) with pilocytic astrocytoma
Close clinico-radiological observation
Progression
Repeat surgery
GTR - gross total resection
NTR - near total resection
TMZ - temozolomide

Fig. 4 Localized/circumscribed glioma (juvenile pilocytic astrocytoma/dysembryoblastic neuroectodermal tumors/ganglioglioma/subependymal giant cell astrocytoma/PXA)

8.1 Circumscribed Gliomas and Glioneuronal/Neuronal Tumors

These are a group of tumors characterized by their low-grade (benign) potential and relatively circumscribed extent. The circumscribed gliomas comprise a diverse histological spectrum with pilocytic astrocytoma being the commonest variant (others being pilomyxoid astrocytoma, subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma [PXA]). Glioneuronal tumors are a separate histological group but clinically most behave and are treated like circumscribed gliomas. These tumors differ from diffuse gliomas by their well-defined delineation, earlier age of onset, lack of invasiveness, and favorable prognosis in many patients. Because of the circumscribed nature of these tumors, they may be amenable to complete resection and eventual cure.

Fig. 5 Adult diffuse glioma (Gr II–III)

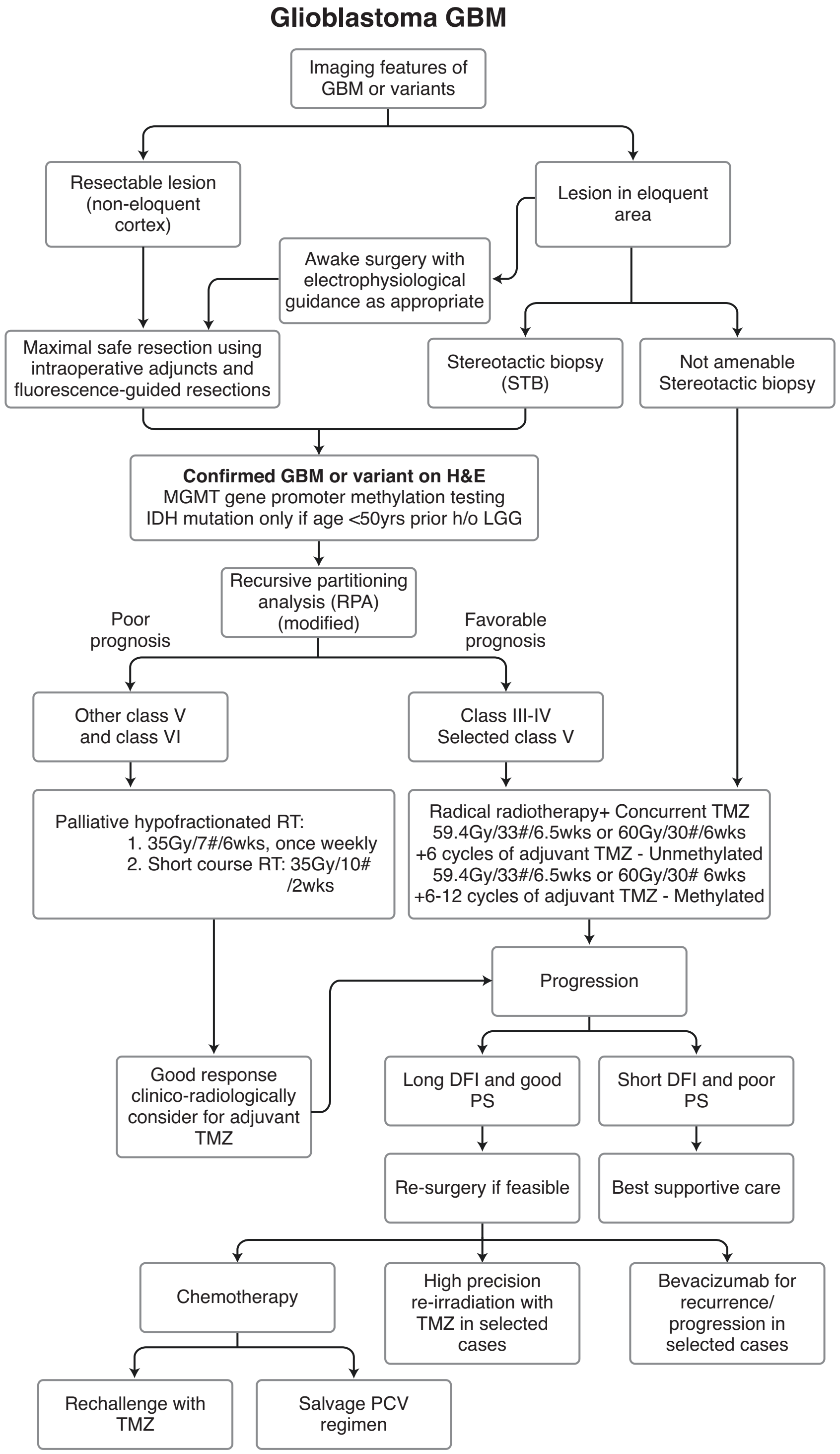

Adult Diffuse Glioma (Gr II-III)
Adult Diffuse Glioma (Gr II-III)
Resectable lesion (non-eloquent area)
Lesion in eloquent area
Maximal safe resection using intra-operative imaging adjuncts
Awake surgery with electrophysiological guidance
GTR/NTR
Debulking large residual tumor
Stereotactic Bx
Not amenable to stereotactic Bx
Histomorphology and grading Molecular diagnosis (IDH mutation and ATRX) Other molecular markers as appropriate
Histomorphology and grading Molecular diagnosis (IDH mutation and ATRX) 1p/19q codeletion for ODG Other molecular markers as appropriate
Confirmed Adult Diffuse Glioma (Gr II-III)
Favourable LGG (Gr II)*
Unfavourable/Aggressive LGG (Gr II)**
Anaplastic (Gr III)
RT+TMZ → 12 cycles adj TMZ (55.8Gy/31#)
RT+TMZ → 12 cycles adj TMZ (59.4Gy/33#)
Observation with clinico-radiological surveillance
Progression without transformation
Repeat surgery if feasible
Progression with transformation to higher grade
Salvage RT+TMZ → 12 cycles adj TMZ Focal conformal technique 54Gy/30#/6wks-55.8Gy/31#
Salvage RT+TMZ → 12 cycles adj TMZ Focal conformal technique 59.4Gy/30#/6½wks

Pignatti's criteria	Favourable*	Unfavourable**
Age	≤40yrs	>40yrs
Neurological deficits	Absent/none	Present
Tumor size	≤6cm	>6cm
Midline	Not crossing midline	Crosses midline
Histology	Oligo component	Astrocytic component
# MIB-1 index	Low	High

Up to 2 unfavourable features qualify as low risk for progression and may be offered close observation with deferred RT at progression

# Not in original Pignatti's criteria, used in institutional practice

Fig. 6 Glioblastoma (GBM)


Glioblastoma GBM
Imaging features of GBM or variants
Resectable lesion (non-eloquent cortex)
Lesion in eloquent area
Awake surgery with electrophysiological guidance as appropriate
Maximal safe resection using intraoperative adjuncts and fluorescence-guided resections
Stereotactic biopsy (STB)
Not amenable Stereotactic biopsy
Confirmed GBM or variant on H&E
MGMT gene promoter methylation testing
IDH mutation only if age <50yrs prior h/o LGG
Recursive partitioning analysis (RPA) (modified)
Poor prognosis
Favorable prognosis
Other class V and class VI
Class III-IV Selected class V
Palliative hypofractionated RT:
1. 35Gy/7#/6wks, once weekly
2. Short course RT: 35Gy/10# /2wks
Radical radiotherapy+ Concurrent TMZ
59.4Gy/33#/6.5wks or 60Gy/30#/6wks
+6 cycles of adjuvant TMZ - Unmethylated
59.4Gy/33#/6.5wks or 60Gy/30# 6wks
+6-12 cycles of adjuvant TMZ - Methylated
Progression
Good response clinico-radiologically consider for adjuvant TMZ
Long DFI and good PS
Short DFI and poor PS
Re-surgery if feasible
Best supportive care
Chemotherapy
High precision re-irradiation with TMZ in selected cases
Bevacizumab for recurrence/ progression in selected cases
Rechallenge with TMZ
Salvage PCV regimen

The primary treatment for circumscribed gliomas is usually maximal safe resection. However, eloquent location frequently precludes complete resection. Radiation is recommended for residual disease in proximity to critical structures (e.g., optico-chiasmatic gliomas) or recurrent/progressive disease that cannot be resected. Conformal techniques to deliver doses ranging from 50 to 54 Gy using dose fractions 1.8 to 2 Gy appear most appropriate. For radiation planning and delineation of tumor, appropriate MR sequences (mostly T2 FLAIR, T2 propeller) need consideration since these tumors are better visible in such sequences. Chemotherapy is often used in younger patients (usually <7 years) with Pilocytic astrocytomas in critical areas (opto-chiasmatic) to achieve tumor control or delay radiotherapy.

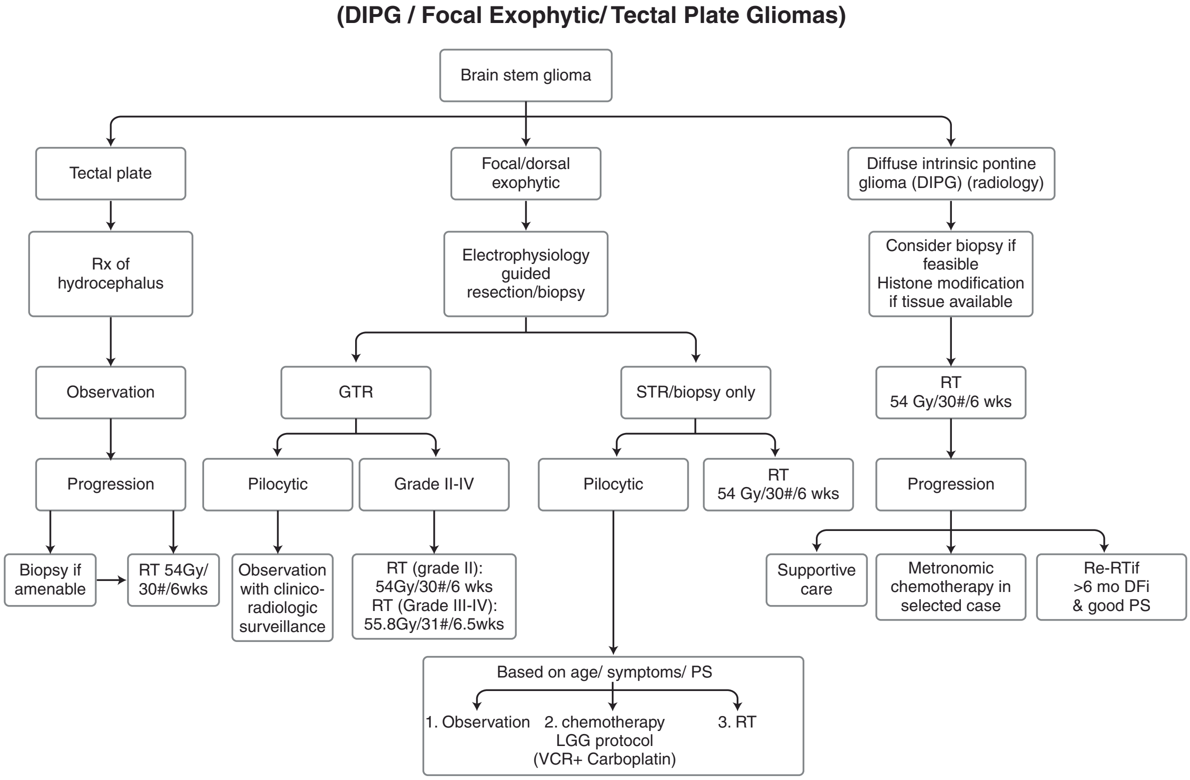
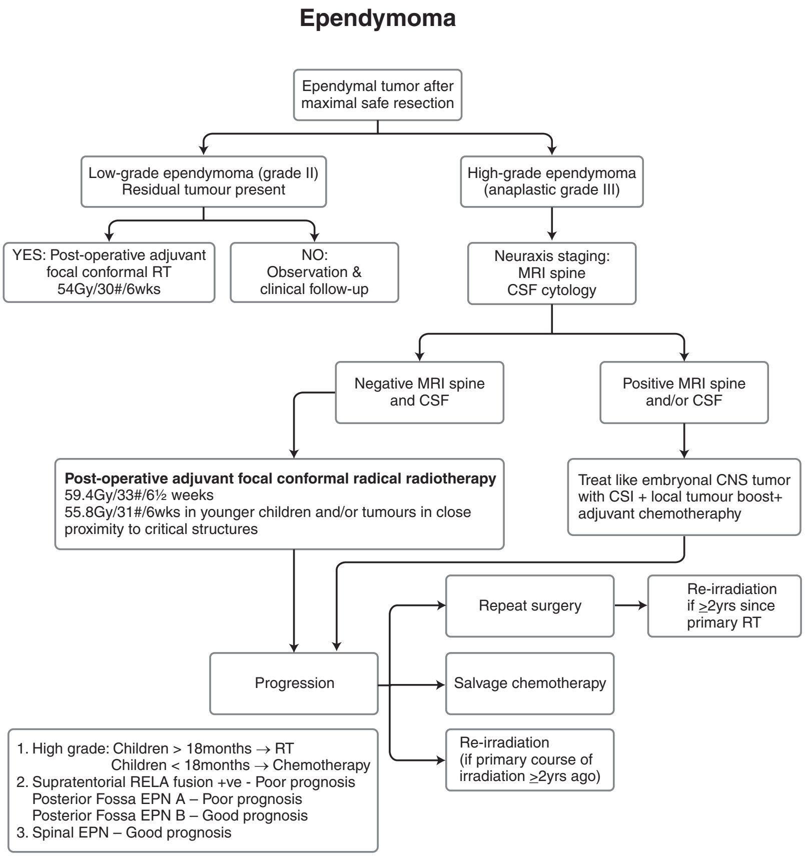

(DIPG / Focal Exophytic/ Tectal Plate Gliomas)
Brain stem glioma
Tectal plate
Focal/dorsal exophytic
Diffuse intrinsic pontine glioma (DIPG) (radiology)
Rx of hydrocephalus
Electrophysiology guided resection/biopsy
Consider biopsy if feasible
Histone modification if tissue available
Observation
GTR
STR/biopsy only
RT
54 Gy/30#/6 wks
Progression
Pilocytic
Grade II-IV
Pilocytic
RT
54 Gy/30#/6 wks
Progression
Biopsy if amenable
RT 54Gy/ 30#/6wks
Observation with clinico-radiologic surveillance
RT (grade II): 54Gy/30#/6 wks
RT (Grade III-IV): 55.8Gy/31#/6.5wks
Supportive care
Metronomic chemotherapy in selected case
Re-RTif >6 mo DFi & good PS
Based on age/ symptoms/ PS
1. Observation
2. chemotherapy LGG protocol (VCR+ Carboplatin)
3. RT

Fig. 7 DIPG/focal exophytic/cervicomedullary/tectal plate gliomas

Fig. 8 Ependymoma


Ependymoma
Ependymal tumor after maximal safe resection
Low-grade ependymoma (grade II)
Residual tumour present
High-grade ependymoma (anaplastic grade III)
YES: Post-operative adjuvant focal conformal RT 54Gy/30#/6wks
NO: Observation & clinical follow-up
Neuraxis staging:
MRI spine
CSF cytology
Negative MRI spine and CSF
Positive MRI spine and/or CSF
Post-operative adjuvant focal conformal radical radiotherapy
59.4Gy/33#/6½ weeks
55.8Gy/31#/6wks in younger children and/or tumours in close proximity to critical structures
Treat like embryonal CNS tumor with CSI + local tumour boost+ adjuvant chemotherapy
Repeat surgery
Re-irradiation if ≥2yrs since primary RT
Progression
Salvage chemotherapy
Re-irradiation (if primary course of irradiation ≥2yrs ago)
1. High grade: Children > 18months → RT
Children < 18months → Chemotherapy
2. Supratentorial RELA fusion +ve - Poor prognosis
Posterior Fossa EPN A – Poor prognosis
Posterior Fossa EPN B – Good prognosis
3. Spinal EPN – Good prognosis

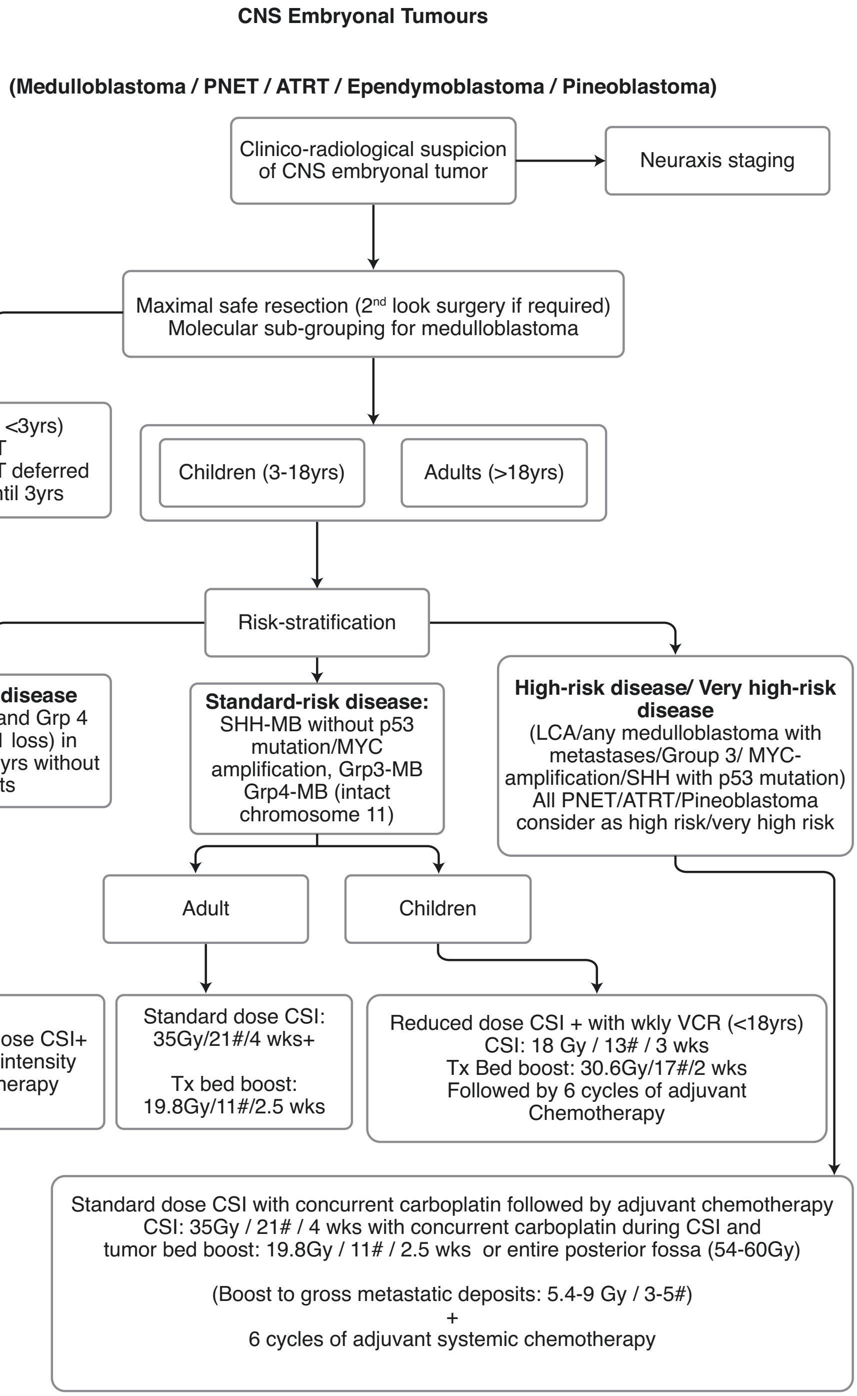
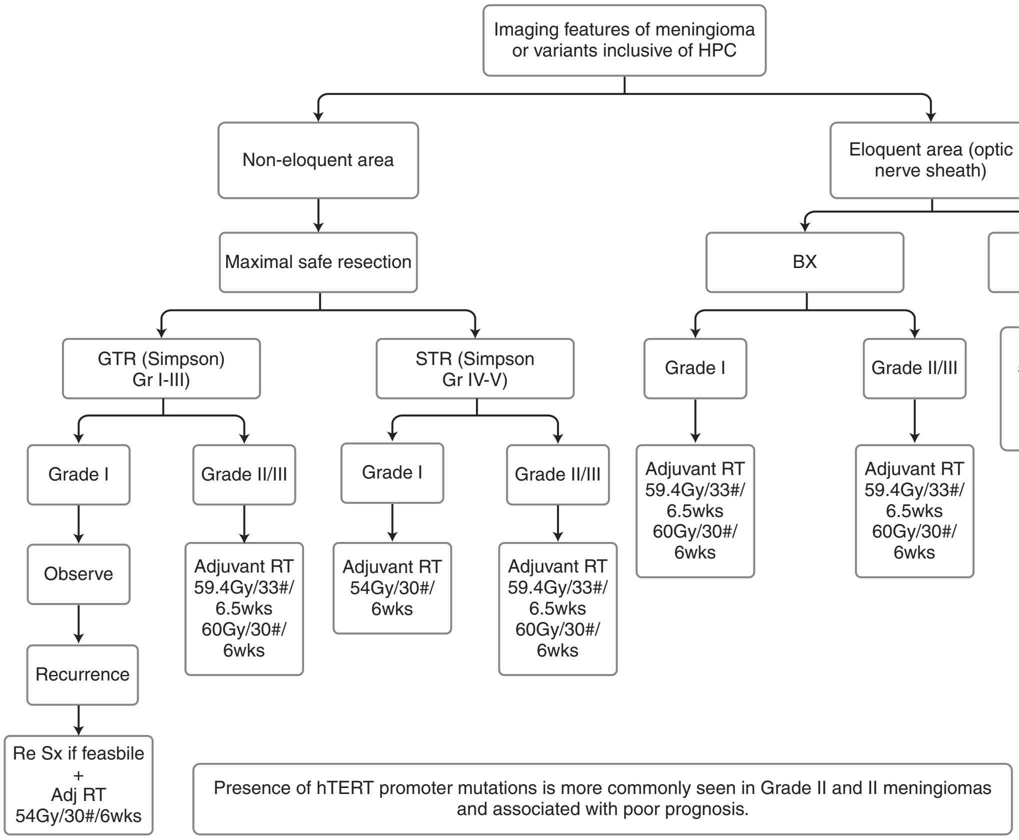

CNS Embryonal Tumours
(Medulloblastoma / PNET / ATRT / Ependymoblastoma / Pineoblastoma)
Clinico-radiological suspicion of CNS embryonal tumor
Neuraxis staging
Maximal safe resection (2nd look surgery if required)
Molecular sub-grouping for medulloblastoma
Infant (Age <3yrs)
1. CT
2. RT deferred until 3yrs
Children (3-18yrs)
Adults (>18yrs)
Risk-stratification
Low-risk disease
(WNT-MB and Grp 4 with Ch 11 loss) in children <16yrs without mets
Standard-risk disease:
SHH-MB without p53 mutation/MYC amplification, Grp3-MB Grp4-MB (intact chromosome 11)
High-risk disease/ Very high-risk disease
(LCA/any medulloblastoma with metastases/Group 3/ MYC-amplification/SHH with p53 mutation)
All PNET/ATRT/Pineoblastoma consider as high risk/very high risk
Adult
Children
Reduced-dose CSI+ Reduced-intensity chemotherapy
Standard dose CSI: 35Gy/21#/4 wks+
Tx bed boost: 19.8Gy/11#/2.5 wks
Reduced dose CSI + with wkly VCR (<18yrs)
CSI: 18 Gy / 13# / 3 wks
Tx Bed boost: 30.6Gy/17#/2 wks
Followed by 6 cycles of adjuvant Chemotherapy
Standard dose CSI with concurrent carboplatin followed by adjuvant chemotherapy
CSI: 35Gy / 21# / 4 wks with concurrent carboplatin during CSI and tumor bed boost: 19.8Gy / 11# / 2.5 wks or entire posterior fossa (54-60Gy)
(Boost to gross metastatic deposits: 5.4-9 Gy / 3-5#)
+
6 cycles of adjuvant systemic chemotherapy

Fig. 9 CNS embryonal tumors (medulloblastoma/PNET/ATRT/ependymoblastoma/pineoblastoma)

Our knowledge regarding the role of BRAF (gene mutation and fusion) in pediatric gliomas has evolved during the last few years. BRAF fusion has a favorable prognosis in pilocytic astrocytoma (70%) and while BRAF V600E mutation has favorable outcomes in PXA [54]. Novel BRAF inhibitors like Vemurafenib and Dabrafenib are under evaluation and may further optimize clinical outcomes in the future. The BRAF pathway is part of the larger complex RAS-RAF-MEK-ERK (MAP Kinase) pathway which is now recognized to be implicated in pediatric type low-grade gliomas, offering opportunities to be targeted using MEK inhibitors.

8.2 Adult Diffuse Gliomas

The term diffuse glioma encompasses the two common histologic subtypes of gliomas that occur in the cerebral hemispheres: diffuse astrocytoma and oligodendroglioma (ODG). The WHO 2021 classification has changed the classification



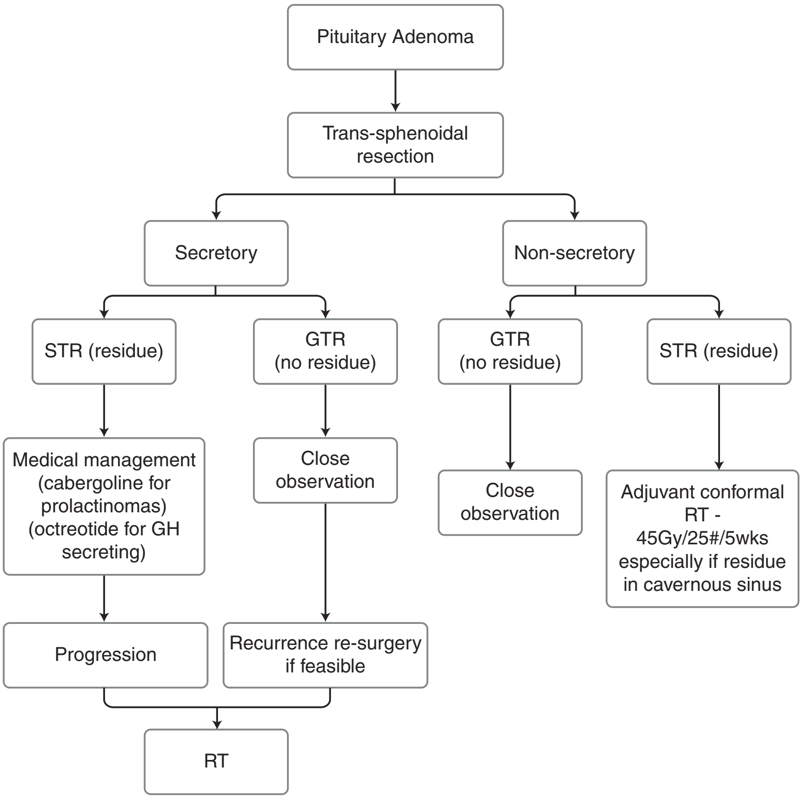
Imaging Features of Meningioma or Variants Including Hemangiopericytoma (HPC)

Imaging features of meningioma or variants inclusive of HPC
Non-eloquent area
Eloquent area (optic nerve sheath)
Maximal safe resection
BX
Not amenable to BX
GTR (Simpson) Gr I-III)
STR (Simpson Gr IV-V)
Grade I
Grade II/III
Direct RT 50.4Gy to 54 Gy/ 28-30# Focal conformal or IG-IMRT
Grade I
Grade II/III
Grade I
Grade II/III
Adjuvant RT 59.4Gy/33#/ 6.5wks 60Gy/30#/ 6wks
Adjuvant RT 59.4Gy/33#/ 6.5wks 60Gy/30#/ 6wks
Observe
Adjuvant RT 59.4Gy/33#/ 6.5wks 60Gy/30#/ 6wks
Adjuvant RT 54Gy/30#/ 6wks
Adjuvant RT 59.4Gy/33#/ 6.5wks 60Gy/30#/ 6wks
Recurrence
Re Sx if feasbile + Adj RT 54Gy/30#/6wks

Presence of hTERT promoter mutations is more commonly seen in Grade II and II meningiomas and associated with poor prognosis.

Fig. 10 Imaging features of meningioma or variants including hemangiopericytoma (HPC)

Fig. 11 Pituitary adenoma



Pituitary Adenoma

Pituitary Adenoma
Trans-sphenoidal resection
Secretory
Non-secretory
STR (residue)
GTR (no residue)
GTR (no residue)
STR (residue)
Medical management (cabergoline for prolactinomas) (octreotide for GH secreting)
Close observation
Close observation
Adjuvant conformal RT - 45Gy/25#/5wks especially if residue in cavernous sinus
Progression
Recurrence re-surgery if feasible
RT

Fig. 12 (**a**) Acoustic Schwannoma. (**b**) NF2 Acoustic Schwannomas

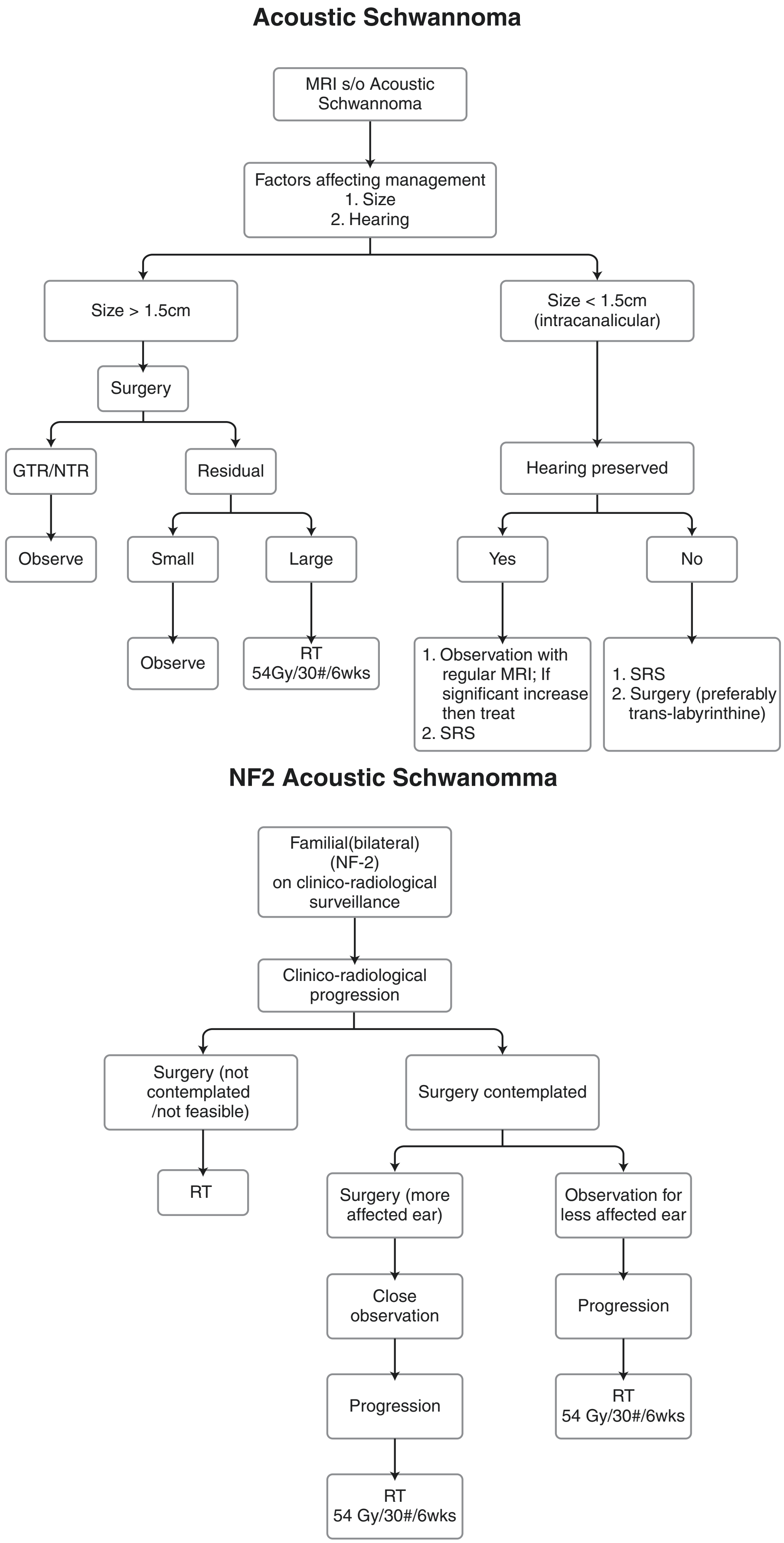
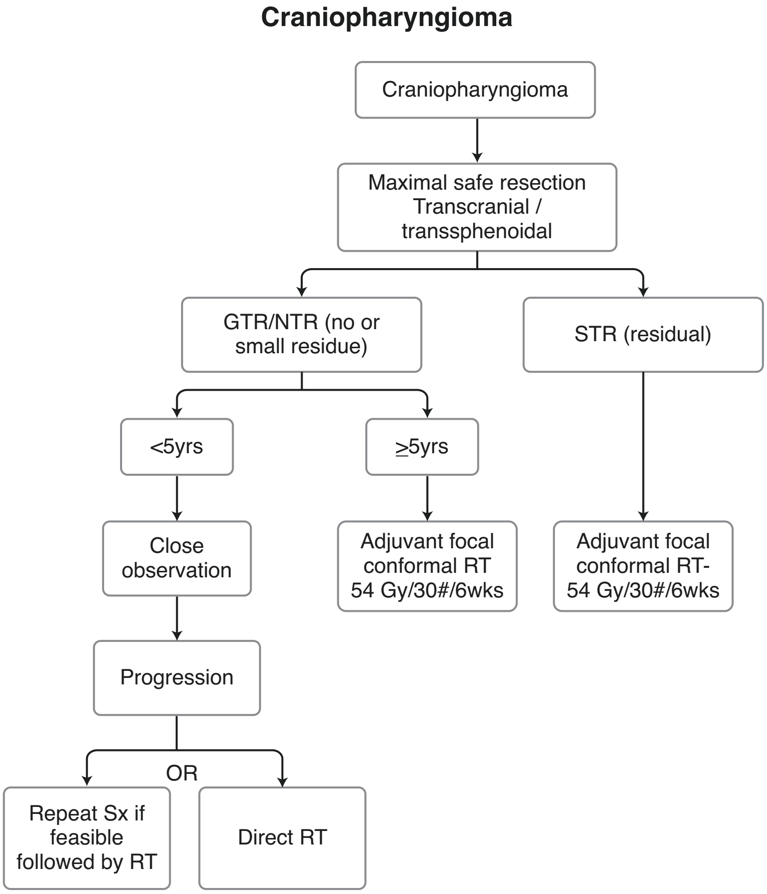

Acoustic Schwannoma
MRI s/o Acoustic Schwannoma
Factors affecting management
1. Size
2. Hearing
Size > 1.5cm
Surgery
GTR/NTR
Observe
Residual
Small
Observe
Large
RT 54Gy/30#/6wks
Size < 1.5cm (intracanalicular)
Hearing preserved
Yes
1. Observation with regular MRI; If significant increase then treat
2. SRS
No
1. SRS
2. Surgery (preferably trans-labyrinthine)
NF2 Acoustic Schwanomma
Familial(bilateral) (NF-2) on clinico-radiological surveillance
Clinico-radiological progression
Surgery (not contemplated /not feasible)
RT
Surgery contemplated
Surgery (more affected ear)
Close observation
Progression
RT 54 Gy/30#/6wks
Observation for less affected ear
Progression
RT 54 Gy/30#/6wks

Fig. 13 Craniopharyngioma

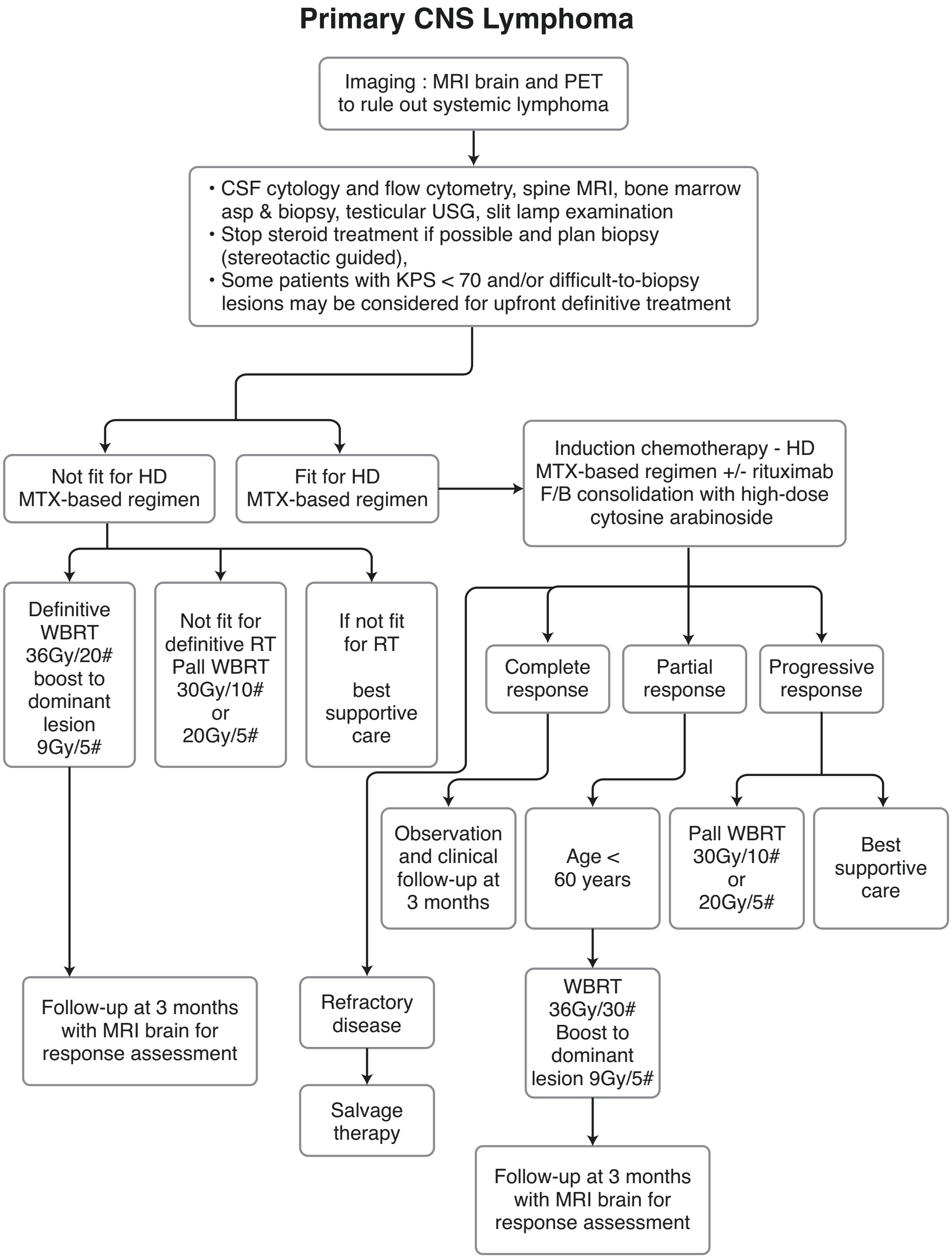

Craniopharyngioma
Craniopharyngioma
Maximal safe resection Transcranial / transsphenoidal
GTR/NTR (no or small residue)
STR (residual)
<5yrs
≥5yrs
Close observation
Adjuvant focal conformal RT 54 Gy/30#/6wks
Adjuvant focal conformal RT- 54 Gy/30#/6wks
Progression
OR
Repeat Sx if feasible followed by RT
Direct RT

and definition of these common tumors. The earlier terminology of mixed glioma/oligoastrocytoma was done away with, being replaced by mandatory molecular characterization in the WHO 2021 classification. This group of tumors which is characterized by IDH (Isocitrate dehydrogenase) mutations are diffuse in nature with an infiltrative growth pattern which may preclude radical resection, especially at eloquent locations. They also have a protracted natural history, which in most instances culminates in transformation into high-grade gliomas. Treatment involves safe maximal resections (or biopsy if not resectable) for histological confirmation followed by adjuvant radiotherapy with or without additional chemotherapy depending upon the histologic and molecular subtypes.

Molecular markers have been incorporated in the new 2021 update of the WHO classification of CNS tumors. IDH mutation testing is a valuable diagnostic, prognostic, and predictive biomarker for the management of patients with glial tumors. IDH1 and IDH2 mutations occur (in a mutually exclusive manner) in nearly 80% of grades II and III oligodendroglioma and astrocytoma and are the defining molecular signature for this group of tumors and a strong prognostic biomarker in patients with glioma, being associated with a favorable outcome. The diagnosis of ODG requires a histological pattern of oligodendroglioma with the demonstration of both an IDH gene family mutation and combined whole-arm losses of 1p and 19q (1p/19q co-deletion). Diffusely infiltrating astrocytomas are genetically defined by the presence of IDH mutations in addition in nearly all cases TP53 mutations as well as, in a large fraction, α-thalassemia/mental retardation syndrome X linked (ATRX) mutations. IDH mutant astrocytic tumors showing histological features of grade 4 or homozygous deletions of CDKN2A/2B behave more aggressively. The WHO 2021 classification has identified pediatric type of diffuse gliomas as distinct from adult diffuse gliomas based on characteristic molecular signatures. These are IDH-wild type, with the high-grade pediatric type diffuse gliomas comprising of the histone altered tumors (see below) including the newly identified histone G34 tumors, and the lower grade ones made of predominantly MAPK pathway-altered tumors. Targeted therapy in pediatric gliomas is therefore an emerging and potentially useful alternative.

Patients with adult diffuse gliomas (WHO grade II astrocytoma or oligodendroglioma) having relatively high mitosis, high Mib-1 index, nuclear pleomorphism suggesting atypical histology for a low grade but not qualifying as grade III tumor on histopathology are known to behave more aggressively. Similarly, radiological features of even subtle but definite gadolinium enhancement and/or considerable

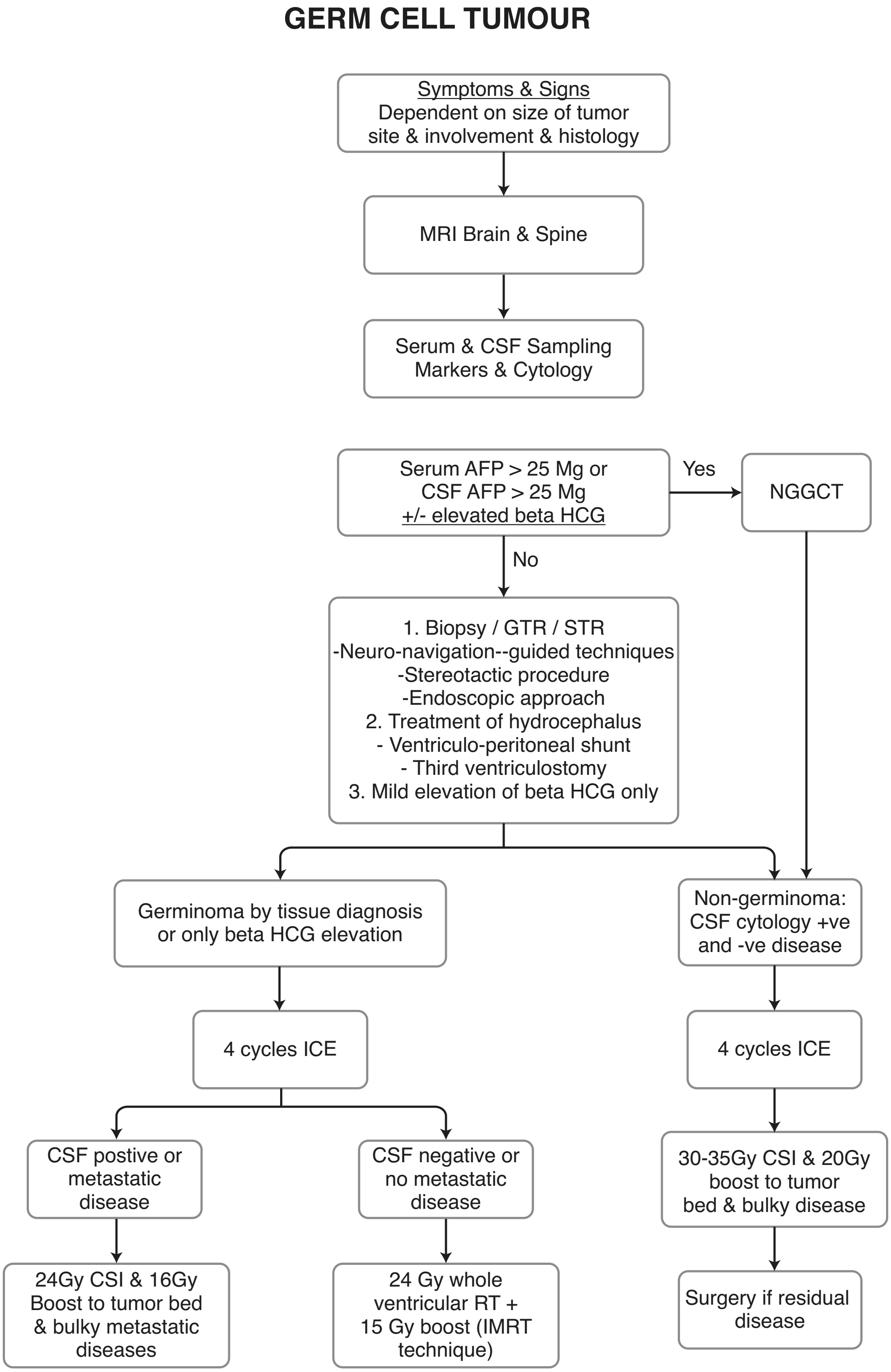
Fig. 14 Primary CNS lymphoma


Primary CNS Lymphoma
Imaging : MRI brain and PET to rule out systemic lymphoma
• CSF cytology and flow cytometry, spine MRI, bone marrow asp & biopsy, testicular USG, slit lamp examination
• Stop steroid treatment if possible and plan biopsy (stereotactic guided),
• Some patients with KPS < 70 and/or difficult-to-biopsy lesions may be considered for upfront definitive treatment
Not fit for HD MTX-based regimen
Fit for HD MTX-based regimen
Induction chemotherapy - HD MTX-based regimen +/- rituximab F/B consolidation with high-dose cytosine arabinoside
Definitive WBRT 36Gy/20# boost to dominant lesion 9Gy/5#
Not fit for definitive RT Pall WBRT 30Gy/10# or 20Gy/5#
If not fit for RT best supportive care
Complete response
Partial response
Progressive response
Observation and clinical follow-up at 3 months
Age < 60 years
Pall WBRT 30Gy/10# or 20Gy/5#
Best supportive care
Follow-up at 3 months with MRI brain for response assessment
Refractory disease
Salvage therapy
WBRT 36Gy/30# Boost to dominant lesion 9Gy/5#
Follow-up at 3 months with MRI brain for response assessment

heterogeneity on T2 fluid-attenuated inversion recovery (FLAIR) sequences are also shown to be adverse prognostic marker. Patients with atypical histology may behave more like an anaplastic variant rather than pure low-grade glioma, and this group may be considered as aggressive low-grade glioma and treated with more intense protocols rather than observation or RT alone.

Surgery alone may not be curative (even if the lesion appears resectable) in patients with most diffuse intermediate-low grade glioma, and additional treatment may be required**.** Post-operative adjuvant treatment is generally required in the event of the presence of adverse factors such as, age ≥40 years, large preoperative tumor size (e.g., ≥5 cm), incomplete resection, astrocytic histology, elevated MIB-1 index (>3%), and absence of a 1p/19q-codeletion [55]. This management approach has been based on evidence gathered from two large cooperative group trials (RTOG 9402 and RTOG 0424 studies) [56–58]. Alkylating chemotherapy using the procarbazine, lomustine, and vincristine (PCV) regimen initially and temozolomide more recently plays an important role in the management of patients with low-grade gliomas. The RTOG 9802 trial compared radiotherapy alone with radiotherapy followed by six cycles of PCV chemotherapy [56].

Fig. 15 Germ cell tumor


GERM CELL TUMOUR
Symptoms & Signs
Dependent on size of tumor
site & involvement & histology
MRI Brain & Spine
Serum & CSF Sampling
Markers & Cytology
Serum AFP > 25 Mg or
CSF AFP > 25 Mg
+/- elevated beta HCG
Yes
NGGCT
No
1. Biopsy / GTR / STR
-Neuro-navigation--guided techniques
-Stereotactic procedure
-Endoscopic approach
2. Treatment of hydrocephalus
- Ventriculo-peritoneal shunt
- Third ventriculostomy
3. Mild elevation of beta HCG only
Germinoma by tissue diagnosis
or only beta HCG elevation
Non-germinoma:
CSF cytology +ve
and -ve disease
4 cycles ICE
4 cycles ICE
CSF postive or
metastatic
disease
CSF negative or
no metastatic
disease
30-35Gy CSI & 20Gy
boost to tumor
bed & bulky disease
24Gy CSI & 16Gy
Boost to tumor bed
& bulky metastatic
diseases
24 Gy whole
ventricular RT +
15 Gy boost (IMRT
technique)
Surgery if residual
disease

Long-term results showed a survival benefit in the group which received radiotherapy and chemotherapy. PFS at 10 years was 51% in the group that received radiation therapy plus chemotherapy versus 21% in the group that received radiation therapy alone; the corresponding rates of overall survival at 10 years were 60% and 40%, respectively. Though widely used, evidence for the use of concurrent and adjuvant temozolomide is awaited from the results of the ongoing CODEL study (NCT00887146). In non-codeleted tumors, the CATNON study has demonstrated the benefit of adjuvant TMZ, though the benefit of concurrent TMZ remains to be seen [59].

Radiation dose is usually between 54 and 59.4 Gy in 30–33 fractions with concurrent TMZ followed by 12 monthly adjuvant TMZ cycles. Grade II aggressive low grade is treated to a dose of 54 Gy in 30 fractions. Grade III tumors require 59.4 Gy in 33 fractions with concurrent TMZ followed by 12 monthly TMZ cycles. However, there is emerging interest in giving 54–55.8 Gy in 31 fractions in co-deleted anaplastic oligodendroglioma.

8.3 Glioblastoma

Glioblastoma is the most common malignant primary brain tumor in adults. As per the 2021 WHO classification, glioblastoma is a diffuse astrocytoma with necrosis and microvascular proliferation and defined by the absence of IDH mutation. For lower-grade IDH wild-type astrocytic tumors, the presence of either EGFR mutation, chromosome 7 loss/10 gain, or TERT promoter mutation, is diagnostic of Glioblastoma. The standard of care for glioblastoma (GBM) is maximal safe surgical resection followed by adjuvant radiotherapy and chemotherapy (temozolomide). Even with the present multi-modality approach, the median survival is around 14–17 months with a high incidence of early recurrence. For the purpose of radiotherapy planning, the gross tumor volume commonly includes the T1-enhanced region with 2 cm clinical target volume and taking into account all relevant T2/Flair abnormality.

The dose and fractionation to be administered generally depend upon the patient's prognosis and performance status:

- Favorable prognosis patients: 59.4–60 Gy in 30 fractions over 6 weeks.
- Poor prognosis/performance patients: 35–40 Gy in 10 fractions over 2 weeks.

Hyper fractionated or hypo-fractionated regimens have not been shown to be associated with survival benefit [60]. Additionally stereotactic radiotherapy boost also has not been shown to prolong survival. In gliomatosis cerebri (a type of diffuse infiltrative high-grade glioma involving more than two lobes of the brain), whole brain radiotherapy to doses of 50 Gy or more achieves disease control in a proportion of carefully selected patients.

Temozolomide is an oral alkylating agent, recommended for concurrent chemo-radiotherapy and adjuvant chemotherapy in patients with glioblastoma [61]. Based on the pivotal phase III trial in which patients with glioblastoma were randomly assigned to postoperative radiation versus radiation plus concurrent temozolomide followed by up to six cycles of adjuvant temozolomide (150 mg/m^2 for first and 200 mg/m^2 for rest of the cycles). They observed that the addition of temozolomide increased the median survival to 15 months vs 12 months with radiotherapy alone.

Bevacizumab is a monoclonal antibody that binds to the vascular endothelial growth factor (VEGF), which plays a critical role in the development of the abnormal vasculature observed in high-grade gliomas and other tumors. Phase II studies using bevacizumab conducted in previously treated patients with high-grade glioma demonstrated a reduction in steroid requirement and imaging evidence of tumor response. These results led to the approval of bevacizumab for recurrent high-grade glioma. The AVAGlio and RTOG 0825 trials exploring bevacizumab versus placebo in the newly diagnosed setting prolonged PFS but not OS, and therefore, it is not a standard of care in the upfront setting.

At recurrence, there is no accepted standard of care and treatment recommendations vary. Management options include repeat surgery or re-irradiation in case of recurrent disease. Second-line systemic therapies, such as anti-angiogenic drugs (bevacizumab), alkylating agents (CCNU), and platinum or newer experimental treatment options like loco-regional injection of replicating viruses, novel chemotherapy agents, epidermal growth factor receptor (EGFR) targeting compounds, or immunotherapy protocols, can be used as per patient requirement.

Combined modality therapy is the standard of care for younger patients with glioblastoma. Toxicity and side effects become more closely balanced with benefits in elderly patients where more convenient shorter courses of radiotherapy (40 Gy in 15 fractions) are commonly used. Recently, the addition of temozolomide (concurrent and adjuvant) to short-course radiotherapy resulted in longer survival than short-course radiotherapy alone, as per a large multi-intuitional randomized controlled trial [62].

Alternating electric fields: A portable medical device applied to the scalp that generates low-intensity alternating electric fields first became available in 2011 for the treatment of recurrent glioblastoma. Experimentally, the biologic activity of the therapy is reported to derive from an anti-mitotic effect imposed by the alternating electric fields, which exert forces on charged tubulin subunits and thereby interfere with the formation of the mitotic spindle. The results of a subsequent open-label randomized trial suggest that the device may improve both progression-free and overall survival when used along with monthly temozolomide in patients with newly diagnosed glioblastoma in the post-radiation setting [63].

Investigational therapies: A variety of therapies are being explored in clinical trials for patients with newly diagnosed glioblastoma. Ongoing studies looking into sub-ventricular zone (SVZ) irradiation and its outcomes have resulted in mixed outcomes and need a carefully done prospective study to evaluate its firm role conclusively [64]. Most studies are testing either molecularly targeted agents or biologic approaches such as immunotherapy, vaccine-based therapies, or local gene therapy. The high expression of checkpoint molecules, in particular, the programmed death ligand-1 (PD-L1) in GBM suggests that PD-L1 can be a good target for further clinical research [65]. H3.3 G34-mutant gliomas is a newly defined high grade (Grade 4) type of glioma classified as pediatric type high-grade glioma (earlier included as glioblastoma), which has a slightly better prognosis than IDH wt glioblastoma and may be amenable to targeted therapy.

8.4 Brainstem and Midline Gliomas

The term brainstem glioma refers to both focal (20%) and diffuse intrinsic (80%) tumors. Patients with diffuse intrinsic tumors typically have a worse prognosis, with a median overall survival of not more than 12 months. Diffuse midline glioma (H3 K27M–altered) is a new entity classified as pediatric type high-grade glioma as per the 2021WHO classification of CNS tumors. The H3 K27M–altered (H3F3A/-HIST1H3B/C) diffuse midline gliomas usually appear histologically as astrocytic tumors. There are clinical situations where there is a clinico-radiological dilemma in midline gliomas (e.g., thalamic) between a low-grade pilocytic and high-grade tumor. Histone mutation status can help achieve correct diagnosis and appropriate management [41].

Given the location of these tumors, surgical resection is usually not possible. Radiation therapy is the only treatment that appears to alter the clinical course of diffuse intrinsic pontine gliomas. Despite multiple trials of dose-escalation, altered fractionation, and radio-sensitization, none of these modulations has been proven more effective than conventionally delivered radiation therapy. Although the degree of tumor shrinkage induced by radiation therapy can be dramatic, the response is generally transient and patients are not cured by this approach. Concurrent chemotherapy has not demonstrated a benefit, nor have other strategies. The identification of novel molecular pathways in diffuse intrinsic pontine gliomas offers the opportunity for their inhibition. The identification of the phospoinositide 3 kinase (PI3K) and sonic hedgehog pathway as possible activating events in xenograft tumors are now being explored as potential targets with molecular therapies [66].

8.5 Ependymal Tumors

Ependymomas are a group of glial tumors that typically arise within or adjacent to the ependymal lining of the ventricular system and account for less than 10% of tumors arising in the CNS. They form a wide spectrum of tumors differing in histology, location, and age groups. They are usually well demarcated with frequent areas of calcification, hemorrhage, and cysts. With improvements in the molecular classification of tumors, genomic data are now being incorporated into the characterization and prognostication of these tumors, for example, RELA fusion-positive (now called ZFTA positive) ependymoma, which predominates in the supratentorial region, have a poor prognosis, are now part of the WHO 2021 update [41]. Surgical resection is usually the first treatment, and the extent of resection is a very important prognostic factor. Radiation is usually considered for grade II ependymal tumors with residual disease post-surgery, grade III histology, and for recurrent tumors. There has been a concern of neurocognitive decline in younger patients (age <3 year), and radiation can be delayed with the use of chemotherapy, especially for supratentorial ependymomas. For grade II ependymoma, 50–55 Gy is delivered using conventional fractionation with a conformal technique. For grade III, higher doses are needed in the range of 55–60 Gy. Few high-grade ependymomas presenting with disseminated metastases may need CSI or an extended field of treatment.

Chemotherapy may have a role in delaying or avoiding postoperative cranial irradiation in children less than 3 years old. There are no randomized trials comparing immediate RT following surgery with a strategy in which surgery is followed by chemotherapy, and RT is deferred. Cisplatin, carboplatin, and etoposide appear to be the most active agents, and higher response rates have been observed with more intense combination regimens. The benefit of adjuvant chemotherapy after surgery and postoperative RT is unclear and needs further evaluation.

8.6 Embryonal Tumors

Embryonal tumors typically occur in infants and young children. The most common tumor in this group are medulloblastomas; other tumor types include embryonal tumor with multi-layered rosettes (ETMR), atypical teratoid/rhabdoid tumors (ATRT), and many new molecularly defined CNS embryonal tumor types, previously called CNS primitive neuro-ectodermal tumor (PNET).

Molecular classification using expression profiling or whole-genome methylation analysis has classified medulloblastoma (MB) into four groups: WNT-activated, SHH-activated, group 3 and group 4 MB with specific demographic, clinico-radiological and prognostic features [67, 68]. Table 1 shows the risk stratification based on these subgroups. A certain overlap between histopathological variants and molecular groups was demonstrated: WNT-activated MBs usually have a classical phenotype, SHH-activated TP53-wild-type tumors often show a desmoplastic/extensive nodularity phenotype, and SHH-activated TP53-mutant tumors and group 3 MB frequently present as large cell/anaplastic

Table 1 Molecular risk stratification in medulloblastomas

Risk groups	Molecular sub-group (histopathologic variant)
Low	WNT-activated MB (classic phenotype) Group 4 MB with chromosome 11 loss or 17 gain
Standard	SHH-activated MB without TP53 mutations/without MYC amplification (desmoplastic/extensive nodularity) Group 3 (large cell/anaplastic) and group 4 (with intact chromosome 11) MB
High/very high	SHH-activated MB with TP53 mutations (large cell/anaplastic) or MYC amplification All groups (except WNT) with metastases

appearance. A number of clinical trials are ongoing to optimize therapies with a view to de-escalate (e.g. lower the RT dose and volume in very favorable WNT pathways) or escalate the therapies in high and very high-risk groups.

Radiation planning and delivery need special care considering the technical challenges associated with cranio-spinal irradiation (CSI) since these tumors are associated with high rates of leptomeningeal seeding. For pediatric patients less than 3 years, radiation is avoided upfront with the use of chemotherapy. For average-risk patients, radiation consists of a reduced dose CSI to a dose of 24–30 Gy using 1.6–1.8 Gy per fraction. Post CSI, the tumor bed in the posterior fossa needs further radiation with a CTV margin of 10–20 mm to receive a total dose of 54–56 Gy. For high risk, a higher dose of CSI is delivered ranging from 30 to 36 Gy followed by boost to tumor bed or entire posterior fossa till 54 to 60 Gy. Metastatic deposits in the brain and spine are also boosted individually after CSI, although the total dose delivered to the spinal disease is limited by its higher radio-sensitivity. The challenge with CSI remains the length of the treatment field which needs to be covered with multiple radiation beams in a linear accelerator increasing dosimetry uncertainties. Quality control is essential with CSI, cautioned by failures reported over field edges (cribriform plates, spinal canal). Similar strategies are followed for other embryonal tumors like PNET, atypical teratoid/rhabdoid tumor (ATRT) with the use of CSI followed by a boost to local sites of disease.

In the standard risk group, reduced doses cranio-spinal irradiation is usually combined with weekly concurrent vincristine and followed by a multidrug regimen that can be cisplatin, vincristine and lomustine, or cisplatin, vincristine, and cyclophosphamide (Packer regimen). Five-year event-free survival (EFS) based on this regimen is over 80%. For high-risk groups, CSI is combined with weekly concurrent carboplatin followed by 6 cycles of a multi-drug regimen consisting of cisplatin, vincristine, and cyclophosphamide.

8.7 Meningioma

Meningiomas account for one-third of the primary CNS tumors in adults with Grade I meningioma accounting for 90%, atypical meningioma 5–7%, and malignant meningioma 1–3% [69]. Surgery remains the mainstay of these tumors with recurrence rates directly related to the extent of resection [70]. However, meningiomas in certain locations (especially skull base) may not be completely resectable. Atypical meningiomas are also associated with high recurrences, and while adjuvant RT is frequently considered for these tumors, optimal timing of its administration is not well established with ongoing studies attempting to define its exact role. Anaplastic meningiomas arise either de novo or may be associated with prior radiation and usually have poor prognosis with recurrence rates 50–94% and overall survival of only 2–5 years. TERT promoter mutation has been shown to have a prognostic relationship with these tumors, with a median time to progression among mutant cases being 10.1 months compared with 179.0 months among wild-type cases [71].

Compared to conventional radiotherapy and three-dimensional conformal radiotherapy, IMRT is useful in tumors close to critical areas, especially the skull base. IMRT delivered by segmental, dynamic, and arc-based IMRT techniques produces equivalent target coverage and avoidance of critical structures, improves local control, and reduces toxicity. Typical RT doses are as follows:

- Grade I: 54 Gy in 30 fractions
- Grade II (atypical meningioma): 55.8–60 Gy in 30–31 fractions
- Grade III (anaplastic meningioma): 60 Gy in 30 fractions

Stereotactic radiosurgery (SRS) may also be considered for recurrent, small, grade I lesions located in close proximity to critical structures with a dose delivered to be between 10 and 14 Gy. Grade II and grade III lesions are generally not suitable for SRS, as the target volume will not encompass the subclinical disease. Most chemotherapeutic agents have minimal or no activity against meningiomas. Agents such as hydroxyurea, dacarbazine, ifosphomide, temozolomide, irinotecan, and alpha-interferons have been studied with negative results. Emerging data suggest that drugs designed to target pathways such as EGFR, mTOR, PDGF, and VEGF involved in cell growth, proliferation, and angiogenesis may prove valuable in therapy.

8.8 Pituitary Adenoma

Optimal management of pituitary adenomas involves surgery, medical therapy, and radiation therapy. Trans-spenoidal resection (endoscopic or microscopic) remains the gold standard for most pituitary adenomas. The goal of surgery is to remove the tumor, relieve compression of the optic apparatus, and achieve biochemical cure (in secretory tumors). The WHO 2021 classification has introduced the new term Pituitary neuroendocrine tumor (PitNET) for these tumors and recommends classifying these tumors by their adenohypophyseal cell lineage using combined immunohistochemical expression of pituitary hormones and transcription factors. Radiation therapy is considered for clinically non-functioning adenomas in the following:

- Residual tumor after surgery. Continued growth is approximately 30–60% at 5 years when adenoma tissue, detected by MRI, remains after surgery [72]. Alternatively, the residual tumor can also be monitored if the patient is not symptomatic and the potential long-term side effects of radiation therapy can be avoided or at least postponed. Residual tumor in cavernous sinus especially mandates consideration for radiation therapy.
- Recurrent tumors: Surgical resection of recurrent tumor is advisable if possible. Even after complete re-excision, the chances of recurrence are about 5% at 5 years and up to 10–25% at 10 years [73]. RT is indicated in these cases (also directly when surgery is not possible/subtotal).

Management of patients with functioning adenomas (acromegaly, Cushings) includes surgical removal of the tumor, RT, and medical management [somatostatin analogs/dopamine agonists]. Surgery remains the initial treatment of choice in these patients with remission rates of 85% for micro-adenomas and 40–50% for macro-adenomas. A good proportion of these patients may require RT/medical management at some point of time in their course to achieve durable local and biochemical tumor control. Radiotherapy may not achieve immediate biochemical control, and often medical management (hormonal) is required to bridge the interim period.

Modern conformal fractionated radiation therapy (IMRT, SCRT, and protons) is generally the preferred mode of therapy for pituitary adenoma with a dose of 45 Gy in 25 fractions at 1.8 Gy daily fractions. In functioning adenomas, the radiotherapy target volume should be the entire sella, which is likely to harbor microscopic extension and such strategies have been shown to be very effective for anatomical and biochemical long-term tumor control [74].

8.9 Acoustic Neuroma

Acoustic neuromas account for approximately 8% of intracranial tumors in adults and 80–90% of tumors of the cerebello-pontine angle. The median age at diagnosis is approximately 50 years. They also occur with NF-2 and may often be bilateral. Various treatment options for acoustic neuroma include observation, surgery alone, and radiation therapy. Older patients with small tumors and limited hearing loss are usually observed with serial imaging and audiometry. However, these patients should be monitored annually for evidence of tumor progression. Surgery generally results in satisfactory long-term control of vestibular schwannomas though a 10-year recurrence rate for partially resected schwannomas can be 20% [75].

Radiation therapy approaches include conventional fractionated radiation therapy, stereotactic radio surgery (SRS), stereotactic radiotherapy, and proton beam therapy. There are no randomized trials comparing different radiation therapy approaches, and data are available from observational studies. Radio surgery (SRS) is a viable treatment option for selected patients with smaller tumors (<3 cm) with PFS at 5 years 90–95%. SRS may be associated with a risk of damage to VII and VIII nerves. It is a treatment option for small tumors who have lost serviceable hearing. Alternately, fractionated stereotactic radiotherapy (SRT) is potentially a better option in which similar tumor control can be achieved with decreased neurotoxicity [76]. Early experience using proton therapy for vestibular schwannoma treatment looks encouraging with 2- and 5-year local control rates of 95% and 94%, respectively. However, long-term follow-up data will be required for usage in routine clinical practice.

8.10 Craniopharyngioma

Craniopharyngiomas are the most common tumors arising from the pituitary region apart from pituitary adenomas. They are commoner in children than adults. These tumors are partly solid and cystic and can have dense areas of calcification. Craniopharyngiomas spark intense reactions from the adjacent brain due to their papillary projections, especially around hypothalamus. This often limits attempts at radical resection (both open and endoscopic). Published literature has revealed good local control in patients where conservative surgery followed by conformal RT protocols is performed for incompletely resected and/or recurrent craniopharyngiomas. This technique also avoids complications of radical surgery. A phase-2 study of conformal RT in midline craniopharyngiomas and low-grade gliomas demonstrated the advantage of using high-precision conformal RT in stabilizing verbal learning and visual auditory learning domains. Completely excised tumors can be observed (local control 85–100% at 5 years). For residual tumors, post-operative conformal RT (SRT/IMRT/Proton beam) to 54 Gy at 1.8-Gy per fraction is preferred (local control 85–100% at 5 years).

8.11 Primary Central Nervous System Lymphoma (PCNSL)

PCNLs are commonly associated with severe immunodeficiency (typically AIDS) and have an inferior prognosis. In the immunocompetent population, PCNSLs typically appear in older patients (median—60 years). High-dose methotrexate therapy in patients with PCNSL is intense, requires close observation, and is considered in patients with good performance status. Standard chemotherapeutic regimens for systemic lymphoma such as CHOP are ineffective in PCNSL, due to poor BBB penetration. Treatment with irradiation and corticosteroids often only produces a partial response, and recurrence is inevitable in more than 90% of patients. It may be considered in palliative setting in patients with poor performance score. Radiation is not recommended in conjunction with methotrexate because of an increased risk of leukoencephalopathy and dementia in patients older than 60 years.

8.12 Germ Cell Tumor

Germ cell tumors (GCTs) constitute 0.4% of all CNS tumors with the incidence of 3.7% in children. They usually occur in the pineal region (as well as sellar-suprasellar and other intraventricular sites). Surgical intervention usually consists of a biopsy to confirm the histopathological diagnosis (in a small subset with negative/equivocal tumor markers) and CSF diversion procedures to relieve the ICP. Non-germinomatous GCTs usually have elevated tumor markers (serum/CSF or both), which obviates the need for histologic diagnosis and the patient can be planned for definitive treatment. CSF cutoff values for NGGCT vary among different treatment groups (Table 2). The prognosis (Table 3) and treatment vary between the different types of GCTs.

Germinoma:

- Four cycles of chemotherapy followed by 40 Gy whole ventricular RT, if CSF-negative and no metastases.
- If CSF-positive or metastatic disease, 4 cycles followed by 24 Gy CSI at 1.5 Gy per fraction and 16 Gy boost to the tumor bed and bulky metastatic sites.

Non-germinomatous germ cell tumor:

- Four cycles of chemotherapy followed by 30–35 Gy CSI at 1.5 per fraction and 20 Gy boost to tumor bed and bulky metastatic sites.
- Surgery if residual disease at the end of therapy.

Table 2 Tumor markers for non-germinomatous germ cell tumors

NGGCT	The United States and Europe Groups	Asian and a few European Groups
CSF and serum AFP	>10 ng/dL	>50 ng/dL
CSF and serum beta HCG	>50 mIU/mL	>100 mIU/mL

Table 3 Prognostication among GCT

Prognostication	
Good	Pure germinoma Mature teratoma
Intermediate	Germinoma with elevated beta-HCG Immature teratoma Teratoma with malignant transformation
Poor	Choriocarcinoma Yolk sac tumor Embryonal carcinoma

8.13 Brain Metastases

Metastases are the most common intracranial tumors in adults (10–30%). Metastases from the lung, breast, melanoma, kidney, and colon are the most common intracranial malignancies. Historically, the overall survival after diagnosis of brain metastasis was poor. However, improvements in systemic disease therapies and multimodality brain metastasis treatment have improved the outcomes in brain metastasis patients. Following factors help in determining the management plan and eventual outcome—status of the primary disease, the extent of systemic burden of the disease, multiplicity of lesions in the brain and resectability, disease-free interval, and molecular targets (if applicable). The primary approaches to the treatment of brain metastases include surgery, stereotactic radiosurgery (SRS), and whole-brain radiation therapy (WBRT). WBRT remains the primary treatment modality for patients with a high intracranial tumor burden. The routine role of WBRT as adjunctive therapy in patients who are candidates for SRS/SRT or surgical resection has evolved. Randomized trials have shown in selected candidates where SRS/SRT is indicated, patients have a better quality of life, especially with regard to neuro-cognition.

9 Patient Reported Outcomes/Quality of Life (QOL)

Quality of life is a multidimensional concept used to measure patients' functioning and well-being. In recent decades, it has become an important outcome measure in clinical trials for brain tumor patients. However, QOL cannot be used alone to outcome measure for assessing the level of functioning and well-being of the patients and alternative tools, such as MD Anderson Symptom Inventory (MDASI) provide a more complete picture of functioning in daily life. Several patient-related, treatment-related, and sociocultural factors influence QOL scores. Various factors influence QOL scores in high-grade gliomas (HGGs) and low-grade gliomas (LGGs) in which the tumor itself appears to be one of the major factors influencing cognitive function and QOL domain scores. Patients with controlled disease have the most preserved QOL domain scores, whereas there are impairments in progression. Other tumor-related factors influencing QOL scores are tumor site, laterality, size, hypothalamic involvement, hormonal deficiencies, and epilepsy. Anticonvulsants, corticosteroids, new neurological deficits, higher dose of radiation therapy, and chemotherapy all have detrimental effects on QOL scores. Complete surgical resection, radiation therapy in HGGs, or low dose per fraction radiation therapy in LGGs with loco-regional control will improve or maintain QOL. The Response Assessment in Neuro-Oncology-Patient-Reported Outcome (RANO-PRO) working group recently highlighted the application of appropriate PRO instruments, with respect to its content and measurement properties (i.e., research question, content validity, and other measurement properties), in brain tumor research to generate high-quality evidence [77]. QOL is increasingly being adopted to determine the cost-effectiveness of various new modalities of treatment in cancer care (e.g., proton beam therapy).

9.1 Survivorship

With improving therapies, patients tend to survive longer. This often exposes them ironically to the consequences of the same therapies (usually radiotherapy) that have prolonged the survival. These toxicities may appear from months to years after radiation is delivered and a majority of them tend to be irreversible. Radio-necrosis is a dose-dependent effect usually affecting mostly during 6 and 24 months in 5–10% of patients in the high-dose region. Other major late sequelae with cranial radiation are neurocognitive decline, endocrinal dysfunction, hearing abnormalities, increased risk of cerebrovascular disease, radiation-induced second malignancies with significant implications on quality of life [78]. Neurocognitive affection in patients with brain tumors is multifactorial contributed by the disease itself, further worsening happening from surgical intervention and adjuvant treatment with radiation and/or chemotherapy. Hypopituitarism may affect 30–90% of patients (all age groups) receiving cranial radiation with deficiencies depending on doses to hypothalamic–pituitary axis [79]. Similarly, sensorineural hearing loss (10–20%, more frequent with doses >35 Gy to cochlea, platinum chemotherapy having an additive role) and increased risk of cerebrovascular events (8–16 times increased risk, higher chances with >40 Gy to circle of Willis) can be reduced by limiting doses to respective organs [80]. Long-term follow-up on a regular basis may help in early identification and treatment like hormonal support for endocrinal deficiencies or psycho-social support.

9.2 Mitigating Adverse Events

Radiation treatment for brain tumors continues to undergo rapid technologic advances with the implementation of highly precise conformal RT techniques such as IMRT, SRS, SRT, and protons, which may minimize the volume of normal tissue receiving high radiation doses. Jalali et al. in a large phase III randomized trial with carefully chosen and clinically relevant endpoints demonstrated that with modern technology tight radiation margins around the tumor can be achieved without compromising on local control and overall survival [81]. Further refinements in proton beam therapy technology using pencil beam scanning and image guidance are likely to further improve the efficacy of radiation therapy. The radiation dose delivered to frontal and temporal lobes has recently emerged as a predictive factor for the late neurocognitive decline. The hippocampus is particularly vulnerable to radiation dose-dependent neurocognitive decline, and whenever possible, hippocampal-sparing radiation is to be delivered [82].

With advances in diagnosis and treatment of brain tumors, survival is growing in number as well as duration. Currently, a lot of emphasis and focus is on advocacy and survivorship issues faced by brain tumor patients. Various international organizations are involved in a wide range of advocacy activities from raising public awareness of the challenges of brain tumors to advocating for equal access to promising new therapies to encouraging the establishment of brain tumor patient and caregiver support groups in countries where they do not exist. They help in collaboration with different government agencies, health professional and cancer organizations, clinicians and research institutes, and patient advocacy organizations around the world. The importance of the role of caregivers has been highlighted as they play a very important role in supporting a person diagnosed with a brain tumor, providing physical, emotional, and practical care depending on the treatment period which may last for a few months or longer.

In conclusion, contemporary neuro-oncology practice with evolving information based on pathology, radiological features, molecular advances, and the complexities of treatment involved, mandates discussion of every case in a multidisciplinary team approach (tumor boards) such that treatment plans incorporating all treatment modalities including modern adjuvant therapies, are optimized for maximum efficacy suiting the needs of the patients.

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Head and Neck Cancers

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Abbreviations

BT	Brachytherapy
EBRT	External beam radiotherapy
EGFR	Epidermal growth factor receptor
FNAC	Fine needle aspiration cytology
HNC	Head and neck cancers
SCC	Squamous cell carcinomas

1 Introduction

Head and neck cancer is synonymous with squamous cell carcinomas (SCC) arising in the mucosa of the head and neck region and is historically associated with the heavy and prolonged use of tobacco. It is a major public health problem worldwide and is responsible for 4.8% of cancer-related deaths globally [1]. Head and neck cancer is comprised of various subsites, which are diverse in their etiology, epidemiology, presentation, and treatment. Though heterogeneous, these subsites are typically discussed together due to similarities in their management. This chapter provides a brief overview of incidence, etiology, and clinical presentation and outlines general principles of management of squamous cell carcinoma of the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, and paranasal sinuses.

2 Incidence and Epidemiology in India and Global

Head and neck cancers (HNC) account for 4.9% of all cancers globally and 19.5% of all cancer incidences in India [1]. It is the second-most common cancer in India with a male-to-female ratio of 3.6:1 and is responsible for 17% of cancer-related deaths in India [1]. It is typically associated with tobacco and alcohol consumption and the observed differences in the incidence of HNC between India and western countries are due to differences in cultural habits (oral tobacco and betel/areca nut usage) [2–5].

The decline in the smoking-related oral cavity and laryngeal cancers in the United States saw a simultaneous increase in oropharyngeal cancers, attributable to increased rates of infection with high-risk human papillomavirus (most commonly subtype 16) [6–8] secondary to an increase in high-risk sexual behaviors. The prevalence of HPV in oropharyngeal SCC ranges between 28% and 68% in the western literature [9, 10], while the Indian data show a lower prevalence (20–22.8%) [11, 12].

Inherited predisposition to SCC of the head and neck may be seen in conditions like Fanconi anemia, Li-Fraumeni syndrome, xeroderma pigmentosum, and ataxia telangiectasia.

The incidence of nasopharyngeal carcinoma is low in most parts of India (<1 per 10,000) and commonly seen in the North-Eastern part of the country with Nagaland state having the highest incidence (21/100,000) for males and Aizawl registry having the highest AARs (5.2/100,000) for females [13, 14].

3 Clinical Presentation in India and Worldwide

Tobacco-related cancers of the oral cavity, larynx, and hypopharynx are typically present in the fifth or sixth decade. In India with oral tobacco usage, the patients present almost a decade earlier [15].

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Table 1 Common presenting symptoms in head and neck cancers

Oral cavity cancer	Oropharynx	Larynx and hypopharynx	Nasal cavity and PNS	Nasopharyngeal cancer
Nonhealing ulcer	Growth/mass	Hoarseness	Nasal obstruction	Painless neck swelling
Exophytic mass	Odynophagia	Change in voice	Epistaxis	Epistaxis
White/red patch	Otalgia	Dysphagia	Proptosis	Nasal obstruction
Per-oral growth	Dysphagia	Weight loss	Per-oral growth	Aural symptoms
Ankyloglossia	Trismus	Stridor	Trismus	Headache
Local pain/ referred to an ear	Large neck nodes—necrotic/conglomerate	Local pain/referred to an ear	Neurological symptoms; headache and cranial nerve deficits	Neurological symptoms; headache, diplopia
Neck swelling		Neck swelling	Neck swelling	Trismus
		Systemic symptoms; due to distant metastases		Systemic symptoms due to distant metastases; bone pain, cough, etc.

HPV-related HNSCC is also seen earlier than tobacco-related cancers. A typical patient with HPV-positive SCCHN is a young male with a median age varying from 54 to 57 years [16–18]. Common presenting symptoms in head and neck cancers are highlighted in Table 1.

An asymptomatic neck mass at presentation without obvious oropharyngeal lesions ('unknown primary') is common in HPV-positive disease, while local symptoms are typical in HPV-negative disease. While distant metastases are uncommon at presentation in most HNCs, higher rates of metastases may be seen in nasopharyngeal, HPV-positive oropharyngeal, and hypopharyngeal cancers.

4 Evaluation and Work-Up

4.1 History

- Disease-related information
- History of habits and addictions
- Medical and family history, including any prior malignancy
- Comorbidity

4.2 Physical Examination

- Performance and nutrition status assessment
- Documentation of the extent of the primary tumor and the neck node (size, number, level)
- Clinical evaluation for inoperability: fixity to underlying structures, extensive dermal edema, skull base, and carotid involvement
- Cranial nerve examination especially in cases of nasopharyngeal and paranasal sinus tumors
- Histological diagnosis—fine needle aspiration cytology (FNAC)/biopsy/slide review

4.3 Endoscopy and Biopsy

- Endoscopy (rigid/flexible) to map the extent of the primary disease and rule out synchronous primary, especially in hypopharyngeal cancers
- Evaluation under anesthesia if the endoscopic evaluation is inadequate
- Biopsy of the lesion for histological confirmation, histological subtype, and grade
- FNAC from the nodes
- Assessment of HPV status in oropharyngeal cancers using the p16 expression
- EBERISH in tissue or measurement of EBV titers for nasopharyngeal cancers
- HPV and EBERISH in metastases of unknown primary

4.4 Radiology

Imaging is essential for most intermediate and advanced cancers for assessment of locoregional extent. Radiological evaluation provides an anatomic tumor map for treatment planning, and prognostication, especially in residual/recurrent disease. CT, MRI, and FDG PET CT have widely used imaging modalities in the current practice for the diagnosis, staging, treatment planning, response evaluation, and follow-up of head and neck cancers.

A contrast-enhanced **CT scan giving a better delineation of cartilage and bone erosion** makes it the imaging of choice for gingivobuccal, laryngeal, and hypopharyngeal cancers. The extent of mandibular erosion is important for planning resection as well as a prognostic criterion. CT also has a complementary role in evaluating paranasal sinuses and skull bases. CT, however, is of limited use in the assessment of perineural spread, dural involvement, and marrow infiltration.

MRI is the preferred modality for imaging the suprahyoid neck which includes the nasopharynx, oropharynx, anterior tongue and hard palate, salivary glands, and paranasal sinuses, owing to its superiority over CT [19] in assessing, primary tumor invasion into surrounding soft tissue and bony structures [20], skull base invasion, intracranial extension, cavernous sinus extension, perineural spread [21], paravertebral space invasion and distinguishing the primary tumor from retropharyngeal lymphadenopathy.

In assessing **cervical nodal metastasis**, CT and MRI have similar sensitivity and specificity, Ultrasound-guided FNAC having the highest sensitivity/specificity for the evaluation of cervical lymphadenopathy [22].

FDG PET-CT is a functional imaging modality that assesses the metabolic status of tumors. It is valuable for response assessment in the post-treatment setting, and for radiotherapy planning, and has a role in evaluating an unknown primary. It is the best modality form metastatic workup in locally-advanced disease, N2, N3 nodes, advanced T stage, and nasopharyngeal and hypopharyngeal cancers which have a high propensity for distant metastasis [23]. PET-CT is a sensitive technique for the identification of distant metastases as well as occult nodal metastasis and is thus superior to CT/MRI in this aspect. PET-CT also has been proven to be superior to CT and MRI in differentiating post-radiation effects from residual/recurrent disease with sensitivities ranging from 88% to 100% and specificities ranging from 77% to 100% and is the imaging modality of choice for post-therapy surveillance [24]. The strength of the PET-CT, especially in the post-treatment setting lies in its high negative predictive value (NPV) [25].

4.5 Pathology

Squamous cell carcinoma is the most common histological subtype across most of the head neck cancer subsites (oral cavity and laryngopharynx), however, in the nasopharyngeal region, the undifferentiated subtype predominates. Table 2 highlights common histological subtypes encountered across

Table 2 Histological subtypes of head and neck cancer

Nasopharynx
– Keratinizing squamous carcinoma: More common in non-endemic areas (up to 25% cases), no association with EBV.
– Non-keratinizing squamous carcinoma: Uncommon variant (<5% of cases).
– Undifferentiated carcinoma: Commonest histology in the endemic population (up to 90%), strong association with EBV.
– Basaloid carcinoma: a rare variant of squamous carcinoma.
– Others: Adenocarcinoma, adenoid cystic carcinoma, salivary origin carcinoma, and clear cell carcinoma.
Oral cavity
– Squamous cell carcinoma: Predominant subtype (up to 90% of cases).
– Verrucous carcinoma: Warty appearance due to excessive keratinization. Low propensity to nodal metastasis. Good prognosis.
– Basaloid carcinoma: An aggressive high-grade variant with poor prognosis.
– Spindle cell carcinoma: A biphasic tumor with squamous and spindle cell components. Low malignant potential.
– Papillary squamous carcinoma: Exophytic, papillary growth. Distant metastases rare. Associated with a good prognosis.
– Others: Adenosquamous carcinoma, carcinoma cuniculatum, salivary gland tumors, sarcomas, and melanomas.
Oropharynx
– Squamous cell carcinoma: Predominant subtype (up to 90% of cases).
– Other variants: Papillary squamous carcinoma, sarcomatoid squamous carcinoma, and basaloid carcinoma.
– HPV-positive oropharyngeal cancer may be associated with poorly differentiated or basaloid variants.
Larynx and hypopharynx
– Squamous cell carcinoma: Predominant subtype (up to 95% of cases).
– Verrucous carcinoma: Slow growing warty growth. Low malignant potential.
– Others: Basaloid carcinoma, spindle cell variant, lymphomas, and sarcoma.
Nasal cavity and PNS
– Squamous cell carcinoma: Most common malignant tumor (up to 50% cases).
– Salivary gland-type carcinoma: Second most common cancer. Adenoid cystic carcinomas are the most common type, characterized by perineural invasion and extensive bone infiltration. Mucoepidermoid carcinoma, Acinic cell carcinoma, clear cell carcinoma, and myoepithelial carcinoma are other types.
– Adenocarcinoma: Third most common of the malignant tumors. Subclassified into intestinal and non-intestinal types.
– Neuroendocrine tumors: Divided according to the different amounts of neuroendocrine differentiation into well-differentiated (typical), moderately differentiated (atypical carcinoids), and poorly differentiated (small and non-small cell types). Sinonasal undifferentiated carcinoma (SNUC) is a distinct pathological entity with undifferentiated characteristics and varying degrees of positivity to epithelial markers and neuroendocrine markers [26].
– Esthesioneuroblastoma: Arises from the olfactory epithelium. Divided into four different pathological grades (Hyam's system) based on the grade of differentiation, the presence of neurofibrillary stroma, and mitotic figures/necrosis. The grade affects prognosis.
– Others: Melanomas, sarcomas, and lymphomas.

(continued)

Table 2 (continued)

Salivary glands
– Pleomorphic adenoma: Accounts for 75% of benign tumors and 90% occur in the parotids. Malignant transformation was rare, seen in longstanding tumors. – Mucoepidermoid carcinoma: Most common malignant tumor of the major salivary glands. Presents as a slow-growing mass. Histological grade and location predict the clinical behavior. – Adenoid cystic carcinoma: More common in the minor salivary glands. A high grade is associated with a poor prognosis. Characterized by extensive soft tissue infiltration, perineural invasion, and late recurrences. – Adenocarcinoma: Usually seen in the elderly. A high grade is associated with a poor prognosis. In general, the prognosis is worse than most other salivary gland tumors. – Acinic cell carcinoma: Low-grade malignancy, presents as a slow-growing mass. Associated with good prognosis. – Malignant mixed tumors: Carcinoma ex-pleomorphic adenoma is the most common type. Usually seen in the elderly. The prognosis depends on the grade and depth of invasion. – Salivary duct carcinoma: An aggressive tumor. Usually seen in the elderly. Most commonly seen in the parotid gland. High propensity for local recurrence as well as distant metastases. – Others: Epithelial-myoepithelial carcinoma, squamous carcinoma, and small cell carcinoma.

Table 3 Synoptic reporting for head and neck cancer

Specimen details	Macroscopic examination	Microscopic examination
• Anatomic site with laterality • Type of specimen • Biopsy: Incision or excision biopsy • Resection: Type of surgery and neck dissection performed • Received fresh/in formalin • Received intact/fragmented • If the frozen section is sent, then the type of specimen for the frozen section	• Specimen description and size • Location/extent/number/**size and thickness** of tumor foci • **Characteristics of tumor**: Polypoidal/sessile/ulceroproliferative/ulcerative • Gross bone/skin involvement if any • Distance of tumor from mucosal, bony, and soft tissue **cut margins** • Neck nodes: Level/number of nodes dissected with the size of largest node and appearance on the cut surface, extra-nodal spread if any	• **Histological subtype of the tumor** • **Grade/differentiation of the tumor** • **The depth of invasion and patterns of invasion** • **Lymphovascular emboli** • **Perineural invasion** • **Bone/skin involvement** • **Status of the margins** • **Neck nodes**: For each level specify, the number of total nodes dissected, the **number of nodes showing metastasis, and extranodal extension (ENE)** • **p16 expression/HPV status** • Nature of frozen section if sent (closest margin, base, inked margin, node, etc.)

various head-neck subsites. The use of the World Health Organization (WHO) classification system is recommended to avoid confusion. Among the head and neck cancers, pathological examination of sinonasal and salivary gland tumors is one of the most challenging owing to the rarity of the disease, the variety of histological types, a broad spectrum of differentiation among the same histological type, and the presence of overlapping pathological features with other entities.

4.6 Histopathological Examination and Reporting (Synoptic Reporting)

There are some common guidelines for histopathological reporting, despite the diverse sites of origin and complex anatomy. The synoptic reporting style captures these guidelines and at the same time remains concise and user-friendly. This kind of reporting enables focus on histological parameters determining prognosis and influencing adjuvant therapies (highlighted in bold in Table 3).

Table 4 Tumor markers in head and neck cancer

Tumor markers	Role
Plasma/serum EBV copy numbers [27–30]	Play an important role in screening, prognosis, and early detection of relapse of nasopharyngeal carcinoma
EBV antiviral capsid antigen IgA	May have a role in the screening and diagnosis of nasopharyngeal cancer
p16 overexpression and HPV DNA	Marker for HPV-positive oropharyngeal cancer which is associated with improved survival compared to HPV-negative oropharyngeal cancers (82.4% vs 57.1% at 3 years, $p < 0.001$) [16]
Androgen receptors, c-kit, HER-2, p53, and Ki-67	Are being investigated as prognostic markers in salivary gland tumors

4.7 Tumor Markers

Important tumor markers in head and neck cancer are highlighted in Table 4.

4.8 Referrals Including Genetic Counseling

There is an emerging role for this in head and neck cancers, especially for patients with multiple primary neoplasms. However, considering the etiological agents responsible for causation, prevention, lifestyle modification, counseling, and tobacco cessation clinics play a vital role.

5 Principles of Management (an Integrated Brief Overview of Treatment Philosophy)

Treatment decisions for all patients should be made in a multidisciplinary clinic with the goal of maximizing survival while preserving form, function, and quality of life. Factors like age, comorbidity, stage, and performance status play a role in deciding the treatment intent.

Treatment modalities for head-neck cancer include surgery, radiotherapy, and chemotherapy. Radiotherapy can be an external beam, brachytherapy, or a combination of external beam and brachytherapy. Chemotherapy is usually administered prior to definitive modalities like surgery or radiotherapy to reduce the bulk of disease (neoadjuvant chemotherapy or induction chemotherapy) or concurrent with radiotherapy to enhance the effect of radiotherapy (chemoradiotherapy) [31, 32].

6 Surgical Management

For patients undergoing planned surgery, a plan should be developed for a tumor-free resection margin and appropriate reconstruction for the restoration of form and function.

6.1 Assessment of Resectability

Tumor involvement in the following structures is considered technically unresectable:

- Involvement of infratemporal fossa above the level of the sigmoid notch of the mandible.
- Erosion of pterygoid plates, sphenoid bone, widening of foramen ovale.
- Extension to nasopharynx or deep extension into eustachian tube or lateral nasopharyngeal wall.
- Encasement of the internal carotid artery, defined as a tumor surrounding the carotids >270°.
- Involvement of mediastinal structures.
- Involvement of prevertebral fascia or cervical vertebrae.

6.2 Principles of Resection

- **En bloc resection** of primary tumor should be performed whenever feasible
  - The third dimension (the base) should be taken carefully into account before excision.
  - An adequate margin of at least 5 mm should be ensured in all directions.
- A frozen section for confirmation of margins may be done if concerned.
- **Neck dissection** should consist of selective neck dissection (Level I–III in the oral cavity and Level II-IV in the larynx and hypopharynx) in a node-negative neck and a modified radical neck dissection (Level I–V) for a node-positive neck. The contralateral neck should be addressed when the probability of bilateral/contralateral metastases is high, e.g., tumors crossing the midline/midline tumors.

6.3 Reconstruction Options

- Mucosal defects:
  - Small defect: Primary closure/local flap/split-thickness skin graft/leave raw according to the site involved.
  - Large defect: Try to replace tissue loss with similar kinds of tissue using pedicle flaps or free flaps.
- Soft tissue loss:
  - Pedicle flaps, e.g., pectoralis major myocutaneous (PMMC) flap, or free flaps, e.g., free radial artery forearm flap (FRAFF) or anterolateral thigh flap (ALT).
- Skeletal defects ± soft tissue and skin loss:
  - Anterior or midline mandibular defects: Free osteocutaneous flaps, e.g., fibula, scapula, iliac bone, and radius (preferred due to better cosmetic and functional outcome)/plate/pedicle flaps.
  - Posterior segment defects: free fibula flap or a PMMC flap (for small defects) may be used.
- Skin defects:
  - Can be covered with local flaps/forehead flaps/deltopectoral flaps/PMMC/free flaps.

6.4 Rehabilitation

- Abstinence from tobacco/alcohol
- Oral hygiene
- Shoulder and neck physiotherapy in all cases of neck dissections
- Bite guide prosthesis following mandibulectomy
- Jaw stretching exercises to prevent post-operative trismus
- Swallowing and speech rehabilitation
- Ophthalmologic and auditory

7 Medical Management

Cisplatin forms the backbone of head and neck chemotherapy regimens, used exclusively for concurrent regimens along with radiotherapy or used in combination with five fluorouracil (doublet regimen) and a taxane (Triplet regimen) for induction regimen [33, 34] prior to definitive therapy. In patients unfit for cisplatin chemotherapy, cetuximab or nimotuzumab [35], which is an epidermal growth factor receptor (EGFR) inhibitor can be used concurrently with radiotherapy [36] (bio-radiotherapy). Table 5 shows commonly practiced head and neck chemotherapy schedules. Table 6 highlights important trials in head and neck cancer.

Table 5 Head and neck chemotherapy schedule

Neo-adjuvant chemotherapy regimens	
TAX 323 regimen [34]	Docetaxel (75 mg/m^2, Day 1), Cisplatin (75 mg/m^2, Day 1) and 5-FU (750 mg/m^2/day continuous IV infusion, Day 1 to Day 5). Repeated every 3 weeks.
TAX 324 regimen [37]	Docetaxel (75 mg/m^2, Day 1), Cisplatin (100 mg/m^2, Day 1) and 5-FU (1000 mg/m^2/day continuous IV infusion, Day 1 to Day 4). Repeated every 3 weeks.
Sun et al. regimen for nasopharynx [38]	Docetaxel (60 mg/m^2, Day 1), Cisplatin (60 mg/m^2, Day 1), and 5-FU (600 mg/m^2/day continuous IV infusion, Day 1 to Day 5). Repeated every 3 weeks.
Concurrent chemotherapy regimens	
Three weekly cisplatin [39]	100 mg/m^2, once every 3 weeks
Weekly cisplatin	40 mg/m^2 once every week
Weekly cetuximab [36]	400 mg/m^2 initial dose followed by 250 mg/m^2 every week
Weekly nimotuzumab [35]	200 mg every week
Weekly cisplatin + nimotuzumab [35]	40 mg/m^2 cisplatin + 200 mg nimotuzumab every week

Table 6 Important trials in head and neck cancer

S. no.	Author/group	Year	n	Design	Endpoint	Results	Comments
Nasopharynx							
1.	Al-Saraf et al. **INT-0099** [40]	1998	147	Ph III RCT RT vs CTRT + ACT	OS PFS	3 year OS: 47% vs 78% ($p = 0.005$) 3 year PFS: 24% vs 69% ($p < 0.001$)	• Poor compliance • Significant proportion had squamous histology • RT alone arm did very poorly than expected
2.	Sun et al. [38]	2016	480	Ph III RCT CTRT vs ICT + CTRT	FFS	3 year FFS: 72% vs. 80% ($p = 0.034$) 3 year OS: 86% vs. 92% ($p = 0.029$) 3 year DMFS 83% vs. 90% ($p = 0.031$)	• Stage III–IVB (except T3–4N0) patients • All patients received RT with IMRT
Postoperative CTRT							
1.	Cooper et al. **RTOG 95-01** [41]	2004	416	Ph III RCT RT vs CTRT	LRC	2 year LRC: 72% vs. 82% ($p = 0.01$) DFS HR = 0.78 ($p = 0.04$) OS difference is not statistically significant	• Included high-risk patients (two or more positive lymph nodes, or ECE, or positive margins)

(continued)

S. no.	Author/group	Year	n	Design	Endpoint	Results	Comments
2.	Bernier et al. **EORTC 22931** [42]	2004	334	Ph III RCT RT vs CTRT	PFS	5 year PFS: 36% vs 47% ($p = 0.04$) OS 40% vs 53% ($p = 0.02$); LRC 69% vs 82% (SS). No difference in DM rate (21% vs. 25%, NS).	• T3–4 any N with negative margins (except T3N0 of the larynx) • T1–2 N2–3 • T1–2 N0–1 with high-risk features (ECE, positive margins, PNI, LVI) • Oral cavity/oropharynx with LN+ at levels IV or V
3.	Pooled data **RTOG 9501/ EORTC 22931** [32]	2005		Pooled analysis		• ECE and positive margins were the only risk factors that had significant benefits with CTRT. • No other factors (2+ lymph nodes, PNI+, LVI+, stage III–IV disease) showed a statistically significant difference	
Neoadjuvant chemotherapy/induction chemotherapy							
1.	Vermorken et al. **TAX 323** [34]	2007	358	Ph III RCT PF vs TPF, followed by RT/AFRT	PFS	Median PFS 8.2 vs. 11 months ($p = 0.007$) Median OS 14.5 vs. 18.8 months ($p = 0.02$)	• Included stage III/IV unresectable head and neck cancer
2.	Posner et al. **TAX 324** [37]	2007	501	Ph III RCT PF vs TPF, followed by CTRT	OS	Median OS: 2.5 vs. 5.9 years ($p = 0.006$) 3 year OS: 48% vs. 62% ($p = 0.006$).	• Included stage III/IV unresectable head and neck cancer
3.	Blanchard et al. **MACH NC** [43]	2013	1772 5 trials	Meta-analysis NACT-3(TPF) vs 2(PF) drug		• Absolute benefit at 5 years: 7.4% in favor of Tax-PF. • TPF was associated with significant reductions in progression, locoregional failure, and distant failure compared with PF.	
Bio-radiotherapy							
1.	Bonner et al. [36]	2006	424	Ph III RCT Cetuximab + RT/AF vs. RT/AF	LRC	• Median LRC: Cetuximab + RT 24.4 months vs RT alone 14.9 months; 3-year LRC: 47% vs. 34% ($p = 0.005$). • Median PFS: 17.1 vs. 12.4 months; 3-year PFS 42% vs. 31% ($p = 0.006$). • Median survival: Median 4.1 vs. 2.4 years; 3-years OS 55% vs 45% ($p = 0.03$).	
2.	Bonner et al. [44]	2010	424	Ph III RCT Cetuximab + RT/AF vs. RT/AF	LRC	• Primary endpoint (LRC) not reported. • 5-year OS 46% vs 36% ($p = 0.018$). • Survival is significantly better if at least grade 2 skin rash. • On subgroup analysis, a benefit for Cetuximab confined to BID or concomitant boost arms only.	
Meta-analysis defining role of chemotherapy							
1.	Pignon et al. **MACH-NC** [31]	2000	10,741 63 trials	IPD meta-analysis	• Absolute survival benefit of 4% at 2 and 5 years in favor of chemotherapy. • There was no significant benefit associated with adjuvant or NACT. • Significant benefits with concurrent chemo (8%), but the heterogeneity of the results prohibits firm conclusions.		
3.	Pignon et al. **MACH-NC** [45]	2009	17,346 93 trials	IPD meta-analysis	• Absolute benefit for chemotherapy of 4.5% at 5 years. • Both direct and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy—the absolute benefit 6.5% at 5 years.		
4.	Pignon et al. **MACH-NC** [45]	2009	16,192 87 trials	IPD meta-analysis Analysis by tumor site	• Chemotherapy benefit was higher for concomitant administration for all tumor locations, but the interaction test between chemotherapy timing and treatment effect was only significant for oropharyngeal and laryngeal tumors and not for oral cavity and hypopharyngeal tumors. • The 5-year absolute benefits associated with the concomitant chemotherapy are 8.9%, 8.1%, 5.4%, and 4% for oral cavity, oropharynx, larynx, and hypopharynx tumors, respectively.		

OS overall survival, *FFS* failure-free survival, *PFS* progression-free survival, *DMFS* distant metastases-free survival, *LRC* locoregional control, *HR* hazard ratio, *RCT* randomized control trial, *IPD* individual patient data, *RT* radiotherapy, *CTRT* chemoradiotherapy, *IMRT* intensity-modulated radiotherapy, *ICT* induction chemotherapy, *ACT* adjuvant chemotherapy, *AFRT* accelerated fractionation radiotherapy, *TPF* docetaxel + cisplatin + fluorouracil, *PF* cisplatin + fluorouracil, *ECE* extracapsular extension, *PNI* perineural invasion, *LVI* lymphovascular invasion, *LN+* lymph node-positive

8 Radiation Management

8.1 Definitive Radiotherapy

Radiation therapy is the preferred modality of treatment in the curative setting for cancers of oropharynx, hypopharynx, and larynx where organ conservation is desired and surgical morbidity is too high. In early stages radiation therapy (definitive RT) is used alone and in advanced stages, radiation therapy is combined with concurrent chemotherapy (definitive chemo radiotherapy) to enhance radiation effects or used as an adjuvant to surgery, with or without concurrent chemotherapy. In nasopharyngeal cancer, radiation therapy is the primary treatment modality owing to the radiosensitive nature of the tumor and very morbid/poor results with surgery. Radiation therapy consists of external beam radiotherapy (EBRT) or brachytherapy (BT) or a combination of both (EBRT + BT) (Table 7).

Doses and volumes in the definitive EBRT setting:

- Primary and involved nodal stations should receive 66–70 Gy equivalent and uninvolved nodes 45–50 Gy.
- Dose/fractionation: 66–70 Gy/33–35 fractions/7 weeks (5 fractions per week). The most commonly used dose-fractionation for RT alone or chemo-radiation. Various other forms of fractionation like accelerated fractionation hyper-fractionation [53] have also been described.
- The dose of cisplatin for chemo-radiotherapy in advanced stages (stage III/IV): Cisplatin 40 mg/m^2 weekly or 100 mg/m^2 every 3 weeks (day 1, 22 and 43) during RT, with hydration and antiemetic prophylaxis.
- The dose of cetuximab for bio-radiotherapy in advanced stage (stage III/IV) patients not fit for cisplatin chemotherapy: 400 mg/m^2 loading dose over 120 min, 1 week prior to commencing radiotherapy, then 250 mg/m^2 weekly during radiotherapy.
- The dose of nimotuzumab for bio-radiotherapy in advanced stage (stage III/IV) patients: 200 mg every weekly. Nimotuzumab can be given as monotherapy in patients not fit or cisplatin along with cisplatin in patients that are fit.

8.2 Brachytherapy

Brachytherapy is a technique of radiotherapy in which radiation sources are placed in or around the tumor. It can be used as a sole modality for definitive RT in the selected early-stage tumor, where the risk of LN involvement is low, or in combination with EBRT to boost the tumor to a higher dose,

Table 7 Important trials in larynx and hypopharynx

S. no.	Author/group	Year	*n*	Design	Endpoint	Results	Comments
1.	Wolf et al. [46] **VA LARYNX TRIAL**	1991	332	Ph III RCT Total laryngectomy + postop RT vs. induction chemo + RT	OS	2-year OS: 68% vs 68% ($p = 0.984$) Larynx preservation: Overall 64%.	– Demonstrated that organ conservation is possible in a significant proportion of patients without affecting survival. – More recurrence at the primary site (12% vs 2%) in the chemo/RT group vs more distant metastases in the surgery group (17% vs 11%).
2.	Lefebvre et al. [47] **EORTC 24891**	2004	202	Ph III RCT Surgery + post-op RT vs induction cisplatin/5-FU + RT	OS	5-year OS 33% vs. 38% 10-year OS 14% vs. 13% 5-year PFS 26% vs. 32%. Larynx preservation 5 years 22%	– This strategy did not compromise disease control or survival (that remained poor) and allowed more than half of the survivors to retain their larynx.
3.	Forastiere et al. [48] **RTOG 9111**	2003	547	Ph III RCT Sequential chemo-RT vs. concurrent chemo-RT vs. RT alone	LP	Larynx preservation: 71% vs. 84% vs. 66% ($p = 0.0001$). Laryngectomy-free survival at 2 years and 5 years—no significant difference ($p = 0.98$) between the two chemo groups but a significant difference between chemo arms and RT alone ($p = 0.011$). No difference in 2 years/5 years OS; distant metastases reduced by chemotherapy	Induction PF followed by RT and CT/RT show similar efficacy for the composite endpoint of LFS. Locoregional control and larynx preservation were significantly improved with concomitant cisplatin/RT compared with the induction arm or RT alone.

(continued)

Table 7 (continued)

S. no.	Author/group	Year	*n*	Design	Endpoint	Results	Comments
4.	Forastiere et al. [49] **RTOG 9111**	2012 10 year update		RCT Sequential chemo-RT vs. concurrent chemo-RT vs. RT alone		10 year update • Chemo arms had significantly higher LFS (laryngectomy-free survival) compared to RT alone arm ($p = 0.03$). No difference in LFS between the two chemo arms. Induction (28.9%) = CTRT arm (23.5%) > RT alone (17.2%). • CTRT arm significantly improved laryngeal preservation rate compared to induction ($p = 0.005$) and RT alone arm ($p < 0.001$). No significant difference between induction and RT alone. CTRT (81%), >induction (67%) = RT alone (63%). • Distant control: Induction (83%), concomitant (83%) > RT alone (76%) for distant control.	
5.	Vermorken et al. **TAX 323** [34]	2007	358	Ph III RCT PF vs TPF, followed by RT/AFRT	PFS	Median PFS 8.2 vs. 11 months ($p = 0.007$) Median OS 14.5 vs. 18.8 months ($p = 0.02$)	Including stage III/IV unresectable head and neck cancer. No comparison with CTRT alone, which is the standard.
6.	Posner et al. **TAX 324** [37]	2007	501	Ph III RCT PF vs TPF, followed by CTRT	OS	Median OS: 2.5 vs. 5.9 years ($p = 0.006$) 3 year OS: 48% vs. 62%, ($p = 0.006$)	Including stage III/IV unresectable head and neck cancer. No comparison with CTRT alone, which is the standard.
7.	Haddad et al. [50] **PARADIGM**	2013	145	Ph III RCT TPF, followed by CTRT vs. CTRT alone	OS	3 Year OS: 73% vs 78% ($p = 0.77$)	Upfront chemoradiation remains the standard of care over induction chemotherapy followed by chemoradiation
Altered fractionation trials							
1.	Overgaard et al. [51] **IAEA-ACC**	2010 Lancet	1008	PH III RCT 5 vs 6 day RT	LRC	5 Years LRC were 30% vs 42% ($p = 0.004$)	A trend toward OS benefit Higher acute toxicities with 6 day RT No increase in late toxicity
2.	Overgaard et al. [52] **DAHANCA 6&7**	2003 Lancet	1485	PH III RCT 5 vs 6 day RT	LRC	5-year LRC 60% vs 70% ($p = 0.0005$). DFS improved (66% vs 73%, $p = 0.01$) but not overall survival.	The benefit was seen for primary tumor control but not nodes. Improved larynx preservation by 80% vs 68%. Increased acute morbidity for the 6-week treatment.
3.	Fu et al. [53] **RTOG 90-03**	2000/2005	1073	SFRT vs HFRT vs Split course AFRT vs AFRT-CB	LRC	HFRT or CB improve LRC ($p = 0.045$ and $p = 0.05$) compared to SFRT A trend for a better OS with HF.	Increased acute effects with all 3. AFX-CB may lead to more grade 3+ late effects.
4.	Bourhis et al. [54] **MARCH**	2006	6515 15 trials	Meta-analysis	Significant survival benefit with altered fractionation, corresponding to an absolute benefit of 3.4% at 5 years ($p = 0.003$). Benefit significantly higher with HF (8% at 5 years) than with AFRT (2% without total dose reduction and 1.7% with total dose reduction at 5 years, $p = 0.02$). There was a benefit on LRC in favor of altered fractionation (6.4% at 5 years; $p < 0.0001$), which was particularly efficient in reducing local failure, than on nodal control.		

OS overall survival, *PFS* progression-free survival, *DMFS* distant metastases, free survival, *LRC* locoregional control, *HR* hazard ratio, *RCT* randomized control trial, *IPD* individual patient data, *RT* radiotherapy, *CTRT* chemoradiotherapy, *ICT* induction chemotherapy, *ACT* adjuvant chemotherapy, *SFRT* standard fractionation RT, *HFRT* hyper-fractionated RT, *AFRT* accelerated fractionation radiotherapy, *CB* concomitant boost, *TPF* docetaxel + cisplatin + fluorouracil, *PF* cisplatin + fluorouracil

to enhance local control. It can also serve as a salvage option in small-volume recurrent disease in combination with surgery or as a lone treatment option.

Lesions suitable for radical brachytherapy include accessible lesions, Small (preferably <3 cm) tumors, Lesions away from the bone, N0 nodal status, and superficial lesions.

Doses used in the brachytherapy setting:

- Radical BT (for T1–T2, N0): 60–70 Gy low dose rate with Iridium-192 or equivalent doses with fractionated high dose rate (e.g., 52 Gy in 13 fractions over 6 days at 4 Gy per fraction b.i.d).

Table 8 Indications for postoperative/adjuvant radiotherapy

Primary	Lymph nodes	Chemo-radiotherapy [32]
– Large primary (pT3/T4) – High-grade tumor – Close/positive margins Relative indications: – Deep infiltrative tumor (DOI) – Lymphovascular invasion (LVE) – Perineural invasion (PNI)	– Bulky nodal disease N2/N3 – Extranodal extension – Multiple-level involvement – Multiple nodes	– Positive resection margin – Extranodal extension (ENE)

- In combination with EBRT (for T1–T3, N0–1): external RT to a dose of 56–60 Gy/28–30#/6 weeks followed by BT boost of 15–20 Gy, low-dose rate, Iridium-192 or 14 Gy in 4 fractions high-dose rate over 2 days (4–3–3–4 Gy).

8.3 Adjuvant Radiotherapy

In other sites like the oral cavity, paranasal sinuses, and salivary glands, where surgery is the preferred modality radiation therapy is used in the adjuvant setting with or without chemotherapy to improve local control and survival. Indications of adjuvant radiotherapy are given in Table 8.

Doses and volumes in the adjuvant setting:

- Primary and involved nodal disease: 56–60 Gy/28–30#/6 weeks, using reducing fields.
- In the presence of R+ resection, site of residual disease, positive cut margins, and ENE: 4–6 Gy boost [55].
- Uninvolved nodal stations: 50 Gy/25#, equivalent.
- The dose of chemotherapy [39] in the adjuvant setting in combination with radiotherapy: Cisplatin 40 mg/m^2 weekly or 100 mg/m^2 every 3 weeks (days 1, 22, and 43) during RT, with hydration and antiemetic prophylaxis.
- Postoperative RT should commence as soon as possible and preferably within 6 weeks. Overall treatment time (OTT) should be kept within 100 days, as prolonged OTT is associated with inferior survival.

9 Site-Wise Management Algorithms

9.1 Nasopharyngeal Cancer

Nasopharyngeal carcinomas are relatively radio and chemosensitive tumors.

Radiotherapy forms the mainstay of treatment of nasopharyngeal carcinomas. Surgery has a very limited role to play in the management of nasopharyngeal carcinomas. Chemotherapy [40] in combination with radiotherapy has been shown to improve survival in advanced nasopharyngeal carcinomas. However, there has been a lack of consensus regarding the optimal sequencing of chemotherapy with radiotherapy.

An earlier meta-analysis [56] showed that concurrent chemoradiation (CTRT) definitely contributes the most towards disease control. However, a significant proportion (22% at 3 years) of patients develop distant metastases after concurrent CTRT necessitating intensification of systemic treatment. Owing to poor compliance (60%) to adjuvant chemotherapy (ACT) after chemoradiation, induction chemotherapy (ICT) is emerging as a preferred means of treatment intensification. Phase II studies have shown good compliance (90%) to ICT with the ability to attain higher doses of the systemic agents and could result in better eradication of distant micro-metastases. A recent randomized trial [38] of induction chemotherapy has shown a survival benefit with the addition of induction chemotherapy to standard CTRT. However, there has been no direct comparison with CTRT followed by the ACT, which is considered the standard of care in some parts. Induction chemotherapy and concurrent chemotherapy schedules are highlighted in Table 6.

With respect to radiotherapy techniques, the current IMRT series enjoy a 3-year locoregional control of over 90% and compared to the 2D technique, IMRT is associated with improvement in local control (especially for late T-stages), Survival [57], and lower incidence of late toxicities (especially delayed xerostomia and late neurological toxicities). Thus, IMRT is the standard treatment technique for NPC.

9.2 Target Volumes and Doses

Target volumes for NPC are based on strong knowledge of patterns of tumor spread as well as patterns of failure. Traditionally, in the 2D era, it extended from the sphenoid sinus superiorly to the clavicle inferiorly, anteriorly including a posterior third of nasal cavity/maxilla, and posteriorly including level V lymph nodes. Contouring target volumes for NPC are derived from these 2D volumes.

9.3 Delineation of GTV

CT, MRI, and PET CT are good imaging modalities for the delineation of GTV. MRI is superior to CT in delineating muscle/soft tissue involvement, and infiltration of the skull base. PET-CT is superior to CT/MRI in the detection of occult nodal/distant metastases; however, underestimates tumors at skull base and cavernous sinuses due to lower resolution compared with MRI. MRI remains the modality of choice for tumor extent delineation. The delineation technique of clinical target volume (CTV) for nasopharyngeal cancer is highlighted in Table 9.

Alternatively, only a high-risk and a low-risk CTV may also be contoured, wherein high-risk CTV and intermediate-risk CTV may be contoured as one single dose level. PTV margins depend on institutional practice. Setup and treatment-related factors influence PTV margins.

Table 9 CTV delineation and doses for nasopharyngeal cancer [58]

High-risk CTV	Gross disease with adequate margins (primary + nodes)	**70 Gy/33#** or 66 Gy/30# or 70 Gy/35#
Intermediate risk CTV	High-risk subclinical region—entire nasopharynx, retropharyngeal nodes, skull base, clivus, pterygoid fossae, PPS, sphenoid sinus, posterior 1/3 nasal cavity and maxillary sinuses to include the pterygopalatine fossae	**59.4 Gy/33#** or 60 Gy/30# or 63 Gy/35#
Low-risk CTV	Uninvolved nodal levels B/L level II–V (level I may not be treated if uninvolved)	**54 Gy/33#** or 54 Gy/30# or 56 Gy/35#

9.4 Management Algorithm for Nasopharyngeal Cancer

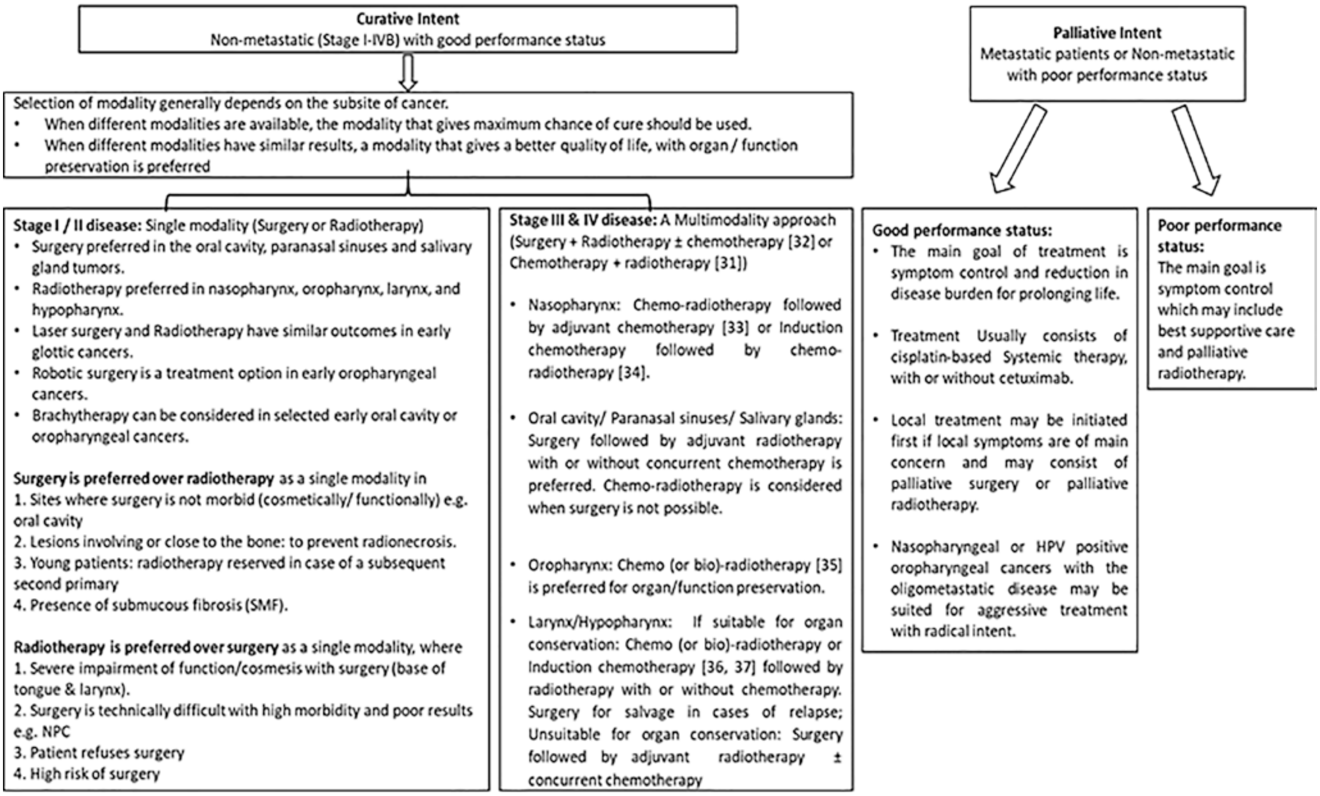
Treatment of NPC depends on the stage of the disease (which can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 107–108, Chapter no. 9, Nasophyarynx, Table: Definition of TNM and AJCC prognostic stage groups and which can be accessed at https://emedicine.medscape.com/article/2048007-overview and Table 10). Radiation alone (IMRT) for stages I and II, and CTRT ± ACT or ICT + CTRT for stages III–IVB diseases is currently considered the standard of care for the management of NPC.

9.5 Oral Cavity

Early-stage oral cavity cancers are typically managed with single-modality therapy (surgery or radiotherapy), while advanced stages are managed with a multimodality approach. Surgery is the preferred modality for resectable, oral cavity cancers; expect early lesions on the lip, angle of mouth, and hard palate. The treatment philosophy behind the selection of one modality over the other has been described in detail in Fig. 1.

Table 10 Management algorithm for nasopharyngeal cancer

<table>
<tr><td colspan="3">Staging workup
• Endoscopic examination and biopsy
• PET-CT
OR
• Chest X-ray
• CT scan/MRI of face, neck, including PNS
• Bone scan especially in WHO type IIB</td><td>Other workup
• EBV titers
• Dental prophylaxis
• Audiometry and visual field testing
• Nutritional counseling
• Thyroid function</td></tr>
<tr><td colspan="4">Treatment algorithm</td></tr>
<tr><td>Stage I (T1 N0)</td><td>Stage II (T2 N0)</td><td>Stage II–IVB (T3–T4 N0 or any T N+)</td><td>Stage IVC (any T any N M1)</td></tr>
<tr><td>– Radical RT alone ± intraluminal BT</td><td>– CTRT</td><td>– ICT + CTRT
– CTRT + ACT
– CTRT alone</td><td>– Individualized treatment should be considered
– Platinum-based doublet or triplet chemotherapy should be used in the first line
– Oligometastatic/good performance status/complete or good responders to chemo should be considered for CTRT + high dose RT to metastasis
– Palliative radiotherapy may be offered to the symptomatic metastatic site or for palliation of progressive locoregional disease</td></tr>
<tr><td colspan="4">Follow-up
– Nasopharyngoscopy and imaging exam (MRI, PET-CT) 12–16 weeks post-RT to evaluate the response
– Follow-up should include an examination of the nasopharynx and neck, cranial nerve function, and evaluation of systemic complaints to identify distant metastasis
– For T3 and T4 tumors, PET-CT/MRI might be used on a yearly basis for at least 5 years
– Evaluation of hormonal function is recommended annually</td></tr>
</table>



Curative Intent
Non-metastatic (Stage I-IVB) with good performance status

Selection of modality generally depends on the subsite of cancer.
- When different modalities are available, the modality that gives maximum chance of cure should be used.
- When different modalities have similar results, a modality that gives a better quality of life, with organ / function preservation is preferred

Stage I / II disease: Single modality (Surgery or Radiotherapy)
- Surgery preferred in the oral cavity, paranasal sinuses and salivary gland tumors.
- Radiotherapy preferred in nasopharynx, oropharynx, larynx, and hypopharynx.
- Laser surgery and Radiotherapy have similar outcomes in early glottic cancers.
- Robotic surgery is a treatment option in early oropharyngeal cancers.
- Brachytherapy can be considered in selected early oral cavity or oropharyngeal cancers.

Surgery is preferred over radiotherapy as a single modality in
1. Sites where surgery is not morbid (cosmetically/ functionally) e.g. oral cavity
2. Lesions involving or close to the bone: to prevent radionecrosis.
3. Young patients: radiotherapy reserved in case of a subsequent second primary
4. Presence of submucous fibrosis (SMF).

Radiotherapy is preferred over surgery as a single modality, where
1. Severe impairment of function/cosmesis with surgery (base of tongue & larynx).
2. Surgery is technically difficult with high morbidity and poor results e.g. NPC
3. Patient refuses surgery
4. High risk of surgery

Stage III & IV disease: A Multimodality approach (Surgery + Radiotherapy ± chemotherapy [32] or Chemotherapy + radiotherapy [31])
- Nasopharynx: Chemo-radiotherapy followed by adjuvant chemotherapy [33] or Induction chemotherapy followed by chemo-radiotherapy [34].
- Oral cavity/ Paranasal sinuses/ Salivary glands: Surgery followed by adjuvant radiotherapy with or without concurrent chemotherapy is preferred. Chemo-radiotherapy is considered when surgery is not possible.
- Oropharynx: Chemo (or bio)-radiotherapy [35] is preferred for organ/function preservation.
- Larynx/Hypopharynx: If suitable for organ conservation: Chemo (or bio)-radiotherapy or Induction chemotherapy [36, 37] followed by radiotherapy with or without chemotherapy. Surgery for salvage in cases of relapse; Unsuitable for organ conservation: Surgery followed by adjuvant radiotherapy ± concurrent chemotherapy

Palliative Intent
Metastatic patients or Non-metastatic with poor performance status

Good performance status:
- The main goal of treatment is symptom control and reduction in disease burden for prolonging life.
- Treatment Usually consists of cisplatin-based Systemic therapy, with or without cetuximab.
- Local treatment may be initiated first if local symptoms are of main concern and may consist of palliative surgery or palliative radiotherapy.
- Nasopharyngeal or HPV positive oropharyngeal cancers with the oligometastatic disease may be suited for aggressive treatment with radical intent.

Poor performance status:
The main goal is symptom control which may include best supportive care and palliative radiotherapy.

Fig. 1 Treatment philosophy and general overview

Resectable cancers are generally treated with surgery ± postoperative radiotherapy/chemo-radiotherapy. The decision regarding adjuvant therapy is usually based on a number of histological parameters previously described in Table 8. The role of intensified treatment for other high-risk factors (lymphovascular invasion, perineural invasion, larger and deeper tumors) needs to be established. Locally advanced tumors involving the masticator space, encasing the carotids, or infiltrating the prevertebral muscles are generally unresectable and are usually managed with chemo-radiotherapy or in certain selected cases Neoadjuvant chemotherapy may be used to shrink the tumor and attempt curative surgery. Staging can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 90–91, Chapter no. 7, Lip and oral cavity, Table: Definition of TNM and AJCC Prognostic Stage Groups which can be accessed at https://emedicine.medscape.com/article/2048034-overview and Table 11 highlights the treatment algorithm for oral cavity cancers. Adjuvant radiotherapy/chemo-radiotherapy indications, radiotherapy doses, chemotherapy schedules, and reconstructive options have been described previously.

9.5.1 Oropharynx

The treatment of oropharyngeal carcinoma is aimed at maximizing cure with minimal functional morbidity. Radical radiotherapy is the treatment of choice in early T1, and T2 tumors, and chemo radiotherapy is the treatment of choice in advanced T3, and T4 tumors. IMRT is the preferred modality of radiotherapy for tumors of the Oropharynx. Surgery is preferred in select early cases where surgical resection is associated with reasonable functional outcomes. It is also preferred with postoperative radiotherapy in select advanced cases, e.g. infiltrative lesions of the base tongue, tonsil, and lesions involving the mandible, and as a salvage procedure for residual neck nodes following chemoradiotherapy.

Transoral resection and neck dissection ± postoperative radiotherapy is gaining popularity for early-stage oropharyngeal cancer especially more so in the HPV-positive setting. Transoral surgery is preferable to open surgery due to lower morbidity and improved function preservation. Various TORS series [59] have reported improved functional outcomes compared to the RT series with this strategy. However, patients with Positive surgical margins and extranodal extension require adjuvant CTRT and Positive margin status can be quite high [60] in some of the series thereby exposing patients to side effects of multiple treatment modalities.

Oropharyngeal primaries have a high predilection for neck node metastases and therefore almost always require elective treatment of cervical lymph node regions at risk of involvement. For the elective treatment of the neck in cN0 patients, irradiation of at least level II-IV is recommended. Elective treatment of the neck usually includes the bilateral

Table 11 Management algorithm for oral cavity cancer

Staging workup • Detailed clinical examination • Examination under anesthesia if the clinical exam is difficult • USG neck for N0 neck • CT scan for the local extent and bone invasion in gingivobuccal complex tumors • MRI is preferred for the tongue and floor of the mouth and for extension in the oropharynx or parapharyngeal space			**Other workup** • Dental prophylaxis • Nutritional counseling • Speech and swallowing evaluation • PET-CT in recurrent case
Treatment algorithm			
Stage I (T1 N0)	**Stage II (T2 N0)**	**Stage III–IVB (T3–T4 N0 or any T N+)**	**Stage IVC (any T any N M1)**
Single-modality therapy: Surgery or RT – Surgery is preferred as it does not involve significant cosmetic/functional deficits. – Radiotherapy is reserved for cases of second primary. – Brachytherapy is a viable option in feasible cases.		Resectable cases: Surgery + adjuvant RT ± chemotherapy with appropriate reconstruction. Unresectable disease: CTRT or induction chemotherapy followed by reassessment for surgery. If the patient is unable to tolerate CTRT, palliative treatment for symptom relief.	– Individualized treatment depending on symptoms. – Palliative radiotherapy may be offered to control loco regional symptoms or for the skeletal metastatic site. – Platinum-based doublet or triplet chemotherapy should be used as the first line systemic therapy in patients with good performance status. – Best supportive care.
Follow-up – Detailed history and clinical examination on each follow-up. – Follow up every 2–3 months for the first 2 years, every 4–6 months for the next 3 years, and annually thereafter. – Rehabilitation: Jaw stretching exercises, dental evaluation, speech, and swallowing therapy. – Routine CT/MRI scans are not recommended: Imaging for suspected locoregional recurrence to assess the feasibility of salvage. – PET-CT scan for suspected, non-accessible recurrences and to rule out distant metastasis. – Biopsy confirmation.			

neck; however, unilateral irradiation [61] may be considered in the well-lateralized tonsillar primary with ≤1 cm mucosal involvement of the base of the tongue or soft palate and N0–N1 nodal status.

PET-CT is the preferred modality for response assessment after chemoradiotherapy with a very high NPV for neck nodes and a moderate NPV for the primary. Patients with a complete response to PET-CT can be kept under surveillance [10].

HPV-positive tumors have improved survival compared to HPV-negative tumors; therefore, several clinical trials are underway, evaluating deintensification strategies in HPV-positive oropharyngeal cancers. However, currently, no difference in treatment recommendations exists, between HPV-negative and HPV-positive tumors.

Staging can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 120, 128–130, Chapter no. 10, HPV-Mediated (p16+) Oropharyngeal Cancer and 11, Oropharynx (p16-) and Hypopharynx Table: Definition of TNM and AJCC prognostic staging groups and which can be accessed at https://emedicine.medscape.com/article/2048285-overview. Table 12 highlights the treatment algorithm for oropharyngeal cancers.

9.5.2 Larynx and Hypopharynx

The management of larynx and hypopharyngeal cancers has seen more changes than any other site amongst head and neck tumors. Since 1991, when the first randomized controlled trial [46] comparing organ preservation versus the gold standard of total laryngectomy in advanced laryngopharyngeal cancers was published, the standards of care have constantly evolved in the past two decades.

Along the way, conservative laryngeal surgery took a new dimension with the acceptance of transoral laryngeal microsurgery as an established treatment option in early laryngopharyngeal cancers. For intermediate-advanced diseases, supracricoid laryngectomy has shown promising results.

In the past 5 years, taxane-based chemotherapy [34, 37] and biological modifiers such as cetuximab [36] and nimotuzumab have improved response rates bringing more moderately advanced laryngopharyngeal cancers into the realm of organ preservation. New technology and altered fractionation regimes have allowed the delivery of optimal radiation dosage and reduced toxicities and morbidity to patients. With the availability of so many treatment options, it is important to evaluate every patient in a multidisciplinary team to decide on the optimal treatment.

For early cancers, both surgery and RT are equally good options for disease control, and the choice of one over the other is essentially driven by the availability of resources and expertise, patient preferences, associated morbidity, and the chance of function preservation or recovery. Laser microsurgery has the advantage of completing the treatment in a single setting and is very effective in very small tumors, however, with larger tumors (e.g., involving both cords), early voice quality may be better with RT.

Table 12 Management algorithm for oropharyngeal cancer

<table>
<tr><td colspan="2">Staging workup
• Detailed clinical/endoscopic examination
• Examination under anesthesia and pan endoscopy if indicated to know the extent of the tumor and assessment for operability
• CT scan for the local extent and nodal staging
• MRI indicated if the base of the tongue is involved or suspected
• PET-CT to rule out distant metastases in patients with large neck nodes or low-level neck nodes</td><td>Other workup
• Biopsy and p16
• Dental prophylaxis
• Nutritional counseling
• Speech and swallowing evaluation</td></tr>
<tr><td colspan="3">Treatment algorithm</td></tr>
<tr><td>Stage I–II</td><td>Stage III–IVB</td><td>Stage IVC, metastatic OPC</td></tr>
<tr><td>• Radical radiotherapy:
– EBRT alone: In most cases. Primary tumor to a dose of 70 Gy/35 fractions or equivalent, low-risk nodal region to 50 Gy equivalent.
– Radical BT: Selected accessible T1 tumors of the soft palate and Tonsil, 50–60 Gy LDR equivalent.
– EBRT + BT: Bulky T2 tumors and BOT tumors, 46–50 Gy EBRT to primary and neck + 20–30 Gy LDR boost.
• Transoral surgery: In selected cases.</td><td>– Chemoradiotherapy.
– Accelerated radiotherapy ± cetuximab if unsuitable for CTRT.
– Primary tumor to a dose of 70 Gy/35 fractions or equivalent, low-risk nodal region to 50 Gy equivalent.
– Surgery reserved for salvage setting.</td><td>– Symptom control and supportive care.
– Palliative radiotherapy may be offered to control loco regional symptoms or for the skeletal metastatic site.
– Platinum-based doublet or triplet chemotherapy should be used as the first line systemic therapy in patients with good performance status.
– HPV-positive patients with oligometastatic disease and good performance status may be treated with more aggressive measures.</td></tr>
<tr><td colspan="3">Follow-up
– Assessment of treatment response with PET-CT at 12–16 weeks.
– Radiological local/nodal residual disease: If biopsy positive and resectable: Salvage surgery or salvage neck dissection. If biopsy positive and unresectable: Palliative chemotherapy. If biopsy negative: Continue follow-up or repeat biopsy if necessary.
– Clinico radiological complete response: Follow up every 2–3 months for the first 2 years, every 4–6 months for the next 3 years, and annually thereafter.
– Routine CT/MRI scans are not recommended: Imaging for suspected locoregional recurrence to assess the feasibility of salvage.
– PET-CT scan for suspected, non-accessible recurrences and to rule out distant metastasis.
– Dental evaluation, speech and swallowing evaluation, audiometry, and thyroid function on follow-up.</td></tr>
</table>

The intermediate-advanced disease is usually treated with a multimodality approach, organ conservation protocols, and non-surgical organ conservation using radiation therapy with chemo/biological therapy or altered fractionation is preferred in most.

Gross cartilage erosion and dysfunctional larynx need to be ruled out in patients being considered for organ conservation strategies.

Resectable cancers are not fit for organ conservation due to gross cartilage erosion or dysfunctional larynx are managed with a total laryngectomy ± pharyngectomy ± esophagectomy and bilateral neck dissection (clearance of levels II-IV in N0 neck and MND in N+ neck) depending on the extent of disease. This needs to be followed by appropriate pharyngeal reconstruction (Folded PMMC or FRAFF ± gastric pull-up are used) as well as voice rehabilitation. Tracheoesophageal speech gives the best voice outcome after total laryngectomy. Tracheoesophageal puncture is preferably performed at primary surgery. Other options include esophageal speech and electrolarynx.

Unresectable cancers are typically managed with chemoradiotherapy ± salvage surgery or Induction chemotherapy followed by reassessment for surgery or CTRT. Induction chemotherapy also plays a role in locally advanced resectable cancers by selecting patients that may benefit from organ conservation. Patients with a complete or partial response after induction chemotherapy warrant radical chemo-radiotherapy as for early disease, while patients with stable disease or progression of disease should preferably be treated with surgery.

Table 6 highlights important trials of organ conservation in the larynx and pharynx. The staging of laryngeal and hypopharyngeal cancer can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 129, 130, 155, and 156, Chapter no. 11; Oropharynx (p16-) and Hypopharynx and Chapter no. 13 Larynx, Table: Definition of TNM staging and AJCC prognostic staging groups and which can be accessed at https://emedicine.medscape.com/article/2048285-overview and https://emedicine.medscape.com/article/2048034-overview and Table 13 shows the treatment algorithm.

Table 13 Management algorithm for laryngeal and hypopharyngeal cancer

Staging workup	**Other workup**
• Detailed clinical/endoscopic (rigid/fibreoptic) examination • CT scan for local extent, cartilage involvement, neck, and retropharyngeal nodes • MRI for early cartilage involvement and base tongue extension • PET-CT to rule out distant metastases in patients with large neck nodes or low-level neck nodes	• Dental prophylaxis • Nutritional counseling • Speech and swallowing assessment is very important to determine the feasibility of organ conservation • Initiate swallowing therapy

Treatment algorithm

Stage I–II	**Stage III (T1–2, N1)**	**Stage III (T3, N0–1)**	**Stage IV (T1–2, N2–3)**	**Stage IV (T3, N2–3)**	**Stage IV (T4, any N)**
Supraglottis – EBRT – Transoral laser microsurgery	**Supraglottis** – CTRT/bio-RT/AFRT – Transoral laser microsurgery with ipsilateral ND + RT ± CT – Supraglottic laryngectomy with bilateral ND + RT ± CT	**Supraglottis** Laryngeal function intact – CTRT/bio-RT/AFRT – Supraglottic laryngectomy with bilateral ND + RT ± CT Laryngeal function compromised – Near-total/total laryngectomy with bilateral ND + RT ± CT	**Supraglottis** – CTRT/bio-RT/AFRT – Transoral laser microsurgery with bilateral ND + RT ± CT – Supraglottic laryngectomy with bilateral ND + RT ± CT	**Supraglottis** Laryngeal function intact – CTRT/bio-RT/AFRT – Supraglottic laryngectomy with bilateral ND + RT ± CT Laryngeal function compromised – Near-total/total laryngectomy with bilateral ND + RT ± CT	**Supraglottis** Intact laryngeal function and framework [exolaryngeal without cartilage destruction] – CTRT/bio-RT/AFRT Laryngeal function and framework compromised [cartilage destruction] – Near-total/total laryngectomy with bilateral ND + RT ± CT
Glottis – EBRT (with small fields) – Transoral laser microsurgery	**Glottis** – CTRT/bio-RT/AFRT – Transoral laser microsurgery with ipsilateral ND + RT ± CT	**Glottis** Laryngeal function intact – CTRT/bio-RT/AFRT – Supracricoid laryngectomy with bilateral ND + RT ± CT Laryngeal function compromised – Near-total/total laryngectomy with bilateral ND + RT ± CT	**Glottis** – CTRT/bio-RT/AFRT – Transoral laser microsurgery with bilateral ND + RT ± CT – Vertical partial laryngectomy with bilateral ND + RT ± CT	**Glottis** Laryngeal function intact – CTRT/bio-RT/AFRT – Supracricoid laryngectomy with bilateral ND + RT ± CT Laryngeal function compromised – Near-total/total laryngectomy with bilateral ND + RT ± CT	**Glottis** Intact laryngeal function and framework [exolaryngeal without cartilage destruction] – CTRT/bio-RT/AFRT Laryngeal function and framework compromised [cartilage destruction] – Near-total/total laryngectomy with bilateral ND + RT ± CT
Subglottis – External beam radiation	**Subglottis** Laryngeal function intact – CTRT/bio-RT/AFRT Laryngeal function compromised – Near-total/total laryngectomy with bilateral (central + lateral) ND + RT ± CT		**Subglottis** – Near-total/total laryngectomy with bilateral (central + lateral) ND + RT ± CT		
Hypopharynx – EBRT (with small fields) – Transoral laser microsurgery	**Hypopharynx** – CTRT/bio-RT/AFRT – Transoral laser microsurgery with ipsilateral ND + RT ± CT	**Hypopharynx** Laryngeal function intact – CTRT/bio-RT/AFRT Laryngeal function compromised – Near-total/total laryngectomy with partial pharyngectomy bilateral ND + RT ± CT – In post-cricoid cases: Total laryngopharyngectomy with bilateral ND with pharyngeal Reconstruction ± esophagectomy + RT ± CT (esophagectomy and gastric pull-up if esophagus involved)	**Hypopharynx** – CTRT/bio-RT/AFRT – Transoral laser microsurgery with bilateral ND + RT ± CT	**Hypopharynx** Laryngeal function intact – CTRT/bio-RT/AFRT Laryngeal function compromised – Near-total/total laryngectomy with partial pharyngectomy bilateral ND + RT ± CT – In post-cricoid cases: Total laryngopharyngectomy with bilateral ND with pharyngeal Reconstruction ± esophagectomy + RT ± CT (esophagectomy and gastric pull up if esophagus involved)	**Hypopharynx** Intact laryngeal function and framework [exolaryngeal without cartilage destruction] – CTRT/bio-RT/AFRT Laryngeal function and framework compromised [cartilage destruction] – Near-total/total laryngectomy with partial pharyngectomy bilateral ND + RT ± CT – In post-cricoid cases: Total laryngopharyngectomy with bilateral ND with pharyngeal Reconstruction ± esophagectomy + RT ± CT

(continued)

Table 13 (continued)

Locally-advanced unresectable disease (T4b any N)	**Metastatic**

• Concurrent CTRT
• Induction chemotherapy is an option in patients with good performance status; followed by response assessment:
  – Partial response: concurrent CRT/radical RT
  – Progressive disease: palliative treatment
• Palliative radiotherapy/chemotherapy or BSC in poor performance status
	– Symptom control and supportive care
	– Palliative radiotherapy may be offered to control loco regional symptoms or for the skeletal metastatic site
	– Palliative chemotherapy in patients with good performance status (platinum + 5-FU + cetuximab; alternatives are platinum doublets with 5-FU or a taxane)
	– Best supportive care in patients with poor performance status

Follow-up Post-organ conservation protocols: – Assessment of treatment response with PET-CT at 12–16 weeks. – **Radiological local/nodal residual disease**: If biopsy positive and Resectable: Salvage surgery or salvage neck dissection. If biopsy positive and Unresectable: Palliative chemotherapy. If biopsy negative: Continue follow-up or repeat biopsy if necessary. – **Clinico radiological complete response**: Follow up every 2–3 months for the first 2 years, every 4–6 months for the next 3 years, and annually thereafter. – Routine CT/MRI scans are not recommended: Imaging for suspected locoregional recurrence to assess the feasibility of salvage. – PET-CT scan for suspected, non-accessible recurrences and to rule out distant metastasis. – Dental evaluation, speech, and swallowing rehabilitation, audiometry and thyroid function on follow-up.	

Neck dissection extent, adjuvant therapies (indications and doses), reconstruction, and rehabilitation as described previously in the previous sections of surgical, medical, and radiation management

CTRT chemo-radiotherapy, *AFRT* accelerated fractionation RT, *ND* neck dissection

9.6 Nasal Cavity and Paranasal Sinuses

Sinonasal malignancies are relatively less common cancers, accounting for <5% of all head-neck malignancies. They are a heterogeneous group of lesions with different sites originating from different histopathologic components. This heterogeneity and the small numbers in each group make it difficult to obtain a high level of evidence in their management.

Newer advances in surgery and radiotherapy have improved survival in these cancers. There is an increasing role of endoscopy in the surgical management of these cases. The standard of care for the treatment of malignancies of the paranasal sinus is craniofacial resection. However, recently the role of endoscopic endonasal resection in the management of these tumors has come to the fore. The endoscopic techniques whether endonasal alone in case of limited disease or combined with open craniotomy have shown encouraging oncological results which are comparable or better to open craniofacial approaches, with significantly reduced morbidity and hospital stay. However, there are definite limitations to the endoscopic approaches.

Absolute contraindications for endoscopic resection:

- Skin involvement
- The anterior wall of maxilla
- Gross brain invasion
- Involvement of the floor of the nasal cavity
- Involvement of lateral or posterior nasopharyngeal walls
- Involvement of the lateral wall of maxilla
- Involvement of the posterior wall of the frontal sinus

In addition, it is imperative that surgeons, who are well-versed and competent with both endoscopic as well as open-surgical approaches, carry out endoscopic resections. Appropriate multilayer reconstruction of the dural defects should be carried out.

Orbital preservation can be attempted in certain cases where there is no invasion of the orbital fat, intraorbital muscles, or orbital apex. One way to plan orbital preservation is to biopsy the orbital fat near the tumor and preserve the orbit only if the fat is negative for tumor infiltration on the frozen section. However, in case of any doubt, it may be oncologically prudent to resect the orbit.

Post-operative radiotherapy is usually indicated in patients with T3–4 tumors, the involvement of adjacent structures like bone, dura, and brain, compromised surgical margins, the presence of lymphovascular invasion, perineural invasion, and positive lymph nodes with or without the extracapsular spread. A dose of 56–60 Gy in patients with a negative margin and 64–66 Gy in patients with positive margins are required. Critical structures surrounding the PNS may limit the delivery of these doses; however, the advent of IMRT with image guidance has definitely improved the dose delivery to these tumors.

Inoperable tumors are typically managed by CTRT or RT alone. Distant metastasis is managed with palliative intent with either chemotherapy or palliative RT to symptomatic sites or best supportive care (BSC) in those with poor performance status.

Neoadjuvant chemotherapy may benefit patients with borderline resectable cases and selected unresectable cases. It is also utilized as an attempt for orbital preservation in selected cases. Cisplatin forms the backbone of neoadjuvant chemotherapy and is combined with different drugs depending upon histology: combination with 5-fluorouracil (5-FU) for ITAC; VP-16 for sinonasal tumors with a neuroendocrine component; doxorubicin for salivary gland tumors; and taxanes and 5-FU for squamous histology. Staging can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 142–143, Chapter no. 12: Nasal Cavity and Paranasal Sinuses, Table: Definition of TNM and AJCC prognostic stage groups which can be accessed at https://emedicine.medscape.com/article/2047703-overview and Table 14 highlights treatment algorithm for nasal cavity and paranasal sinus cancers.

Table 14 Management algorithm for paranasal sinuses

Staging workup • Detailed endoscopic examination and biopsy • CT scan—preferred for osseous involvement, the floor of the anterior cranial fossa, and orbital walls • MRI preferred for an intracranial extension, perineural spread, post-surgery setting, differentiation between retained secretions and tumor tissue • PET-CT to rule out distant metastases in patients with aggressive histologies and high-grade tumors	**Other workup** • Dental prophylaxis • Ophthalmological evaluation • Endocrine evaluation	
Treatment algorithm nasal cavity and ethmoid sinuses		
T1–T2	**T3–T4a**	**T4b**
• Surgery ± post-operative radiotherapy – Approaches: Midfacial degloving or lateral rhinotomy or endoscopic transnasal – Medial maxillectomy with ethmoidal clearance may be adequate for localized ethmoidal and nasal cavity tumors – Neck dissection in N+ neck – RT in case of margin positivity or perineural spread. Dose: 54–60 Gy • Radical radiotherapy preferred if surgical resection is morbid/patients are unfit or unwilling for surgery. Dose: 60–66 Gy.	• Surgery + adjuvant RT (concurrent chemo as per Indication) – Total Maxillectomy with ethmoidectomy – Combined craniofacial approach for lesions reaching/involving the cribriform plate – Orbital exenteration if eye involved – Neck dissection in N+ neck	– Concurrent CTRT – Resection in a very select group with favorable histology with low biologically aggressive tumors for, e.g. adenoid cystic carcinoma, basal cell carcinoma – Neck dissection in N+ neck – Poor PS: Best supportive care
Treatment algorithm maxillary sinuses		
T1–T2	**T3–T4a**	**T4b**
• Surgery + post-op radiotherapy – Infrastructure maxillectomy – Maxillectomy with orbital plate preservation – RT in case of margin positivity or perineural spread or adenoid cystic histology – Neck dissection in N+ neck	• Surgery (primary and neck) + post-op RT (concurrent chemo as per indication) – Total maxillectomy with ethmoidectomy in T3 – Combined craniofacial resection in T4 – Orbital exenteration if eye involved – NACT can be considered if orbital preservation to be attempted or in borderline resectable cases	– Concurrent CTRT – Resection in a very select group with favorable histology with low biologically aggressive tumors for, e.g. adenoid cystic carcinoma, basal cell carcinoma – Poor PS: best supportive care
Post-maxillectomy reconstruction: – If palatal defect is less than one-third: obturator preferred. – Sling if orbital floor excised, to prevent post-op diplopia. Fascial sling is preferred over muscle. Titanium mesh may be used. – Microvascular free tissue transfer for • Extensive skin and soft tissue defect • More than half of palatal loss • Orbit resection • Skull base reconstruction – Temporary obturator for 2–3 months till complete contracture occurs. – Final maxillary prosthesis after 2–3 months.	**Follow-up** • Regular follow-up as usual for all head-neck malignancies. • Follow up every 2–3 months for the first 2 years, every 4–6 months for the next 3 years and annually thereafter. • Surveillance is to be done using an endoscope. • Baseline post-treatment imaging (MRI preferred) to be done 3 months after completion of treatment. • Follow-up imaging with MRI is recommended annually for at least 2 years, thereafter when symptomatic. • In case of a cavity closed by a free flap, surveillance with MRI is recommended. • Dental evaluation, speech and swallowing evaluation, ophthalmological evaluation, and thyroid function on follow-up.	

9.7 Salivary Gland Tumors

Treatment recommendations are based on retrospective reviews of clinical experience, and there are almost no data from randomized trials to guide treatment decisions. Surgery is the mainstay of treatment for resectable, non-metastatic salivary gland tumors. The surgical approach and the extent of resection depend upon the location and extent of the tumor (see Table 15). Facial nerve monitoring is a useful aid to identify the nerve during surgery. However, practice varies widely across the world and it is yet to be considered as a standard of care, there is a significant reduction in immediate post-operative paralysis but not in permanent facial nerve impairment. Also, the benefit of using the nerve monitor is greater in recurrent cases. Neck dissection is done in all cases with cN+ Neck and in cN0 neck with certain high-risk features (grade, extraparenchymal extension, high-risk histologies, and size).

Early-stage, low-grade malignancies including low-grade mucoepidermoid carcinomas, acinic cell carcinomas, and

Table 15 Management algorithm for salivary gland tumors

Staging workup	**Other workup**
• History and physical examination • FNAC: Safe and effective with high sensitivity and specificity • Core biopsy: May be considered where an initial FNA is either inconclusive or equivocal • USG: Simple and inexpensive, however, not comprehensive enough for assessing the deep lobe of the parotid or parapharyngeal space • CT scan: Where bone destruction is suspected at the skull base or o suspected involvement of the mandible and to assess neck nodes • MRI: Better soft tissue delineation, delineation of the interface between tumor and normal salivary gland, better imaging of the parapharyngeal space, perineural spread, and facial nerve status	• Neurological testing for facial nerve • Dental prophylaxis
Treatment algorithm	
Parotid gland	**Submandibular gland**
• Benign parotid tumors – Superficial parotidectomy or partial parotidectomy for benign tumors of the superficial lobe – Total conservative (nerve-sparing parotidectomy): For larger tumors and tumors involving deep lobe • Malignant tumors – Superficial parotidectomy for early (T1–T2) low-grade malignant tumors of superficial lobe – Total parotidectomy in high-grade malignant tumors, T3–4 tumors, Tumours with extraparenchymal spread, and malignant tumors of the deep lobe – Facial nerve sacrifice is done if there is preoperative or intraoperative evidence of involvement. Clear margins at both ends need to be ensured. Mastoidectomy and exploration of the intratemporal part of the facial nerve may be required to achieve a negative proximal stump. This may be followed by facial nerve reconstruction using a nerve graft. – If there is an extension beyond the parotid, the surgery may extend to involve resection of the skin, mandible, mastoid, temporal bone, or infratemporal fossa followed by appropriate reconstruction.	• En bloc resection of the gland with SOHD and any involved structure in the submandibular triangle • Resection may extend to the floor of the mouth and mandible • In adenoid cystic carcinoma: Excision of the hypoglossal and lingual nerves may be needed if intraoperative thickening is noticed
• Management of neck: Ipsilateral neck dissection (MND) is the standard for a cN+ neck. Selective neck dissection (SOHD) may be warranted for cN0 neck in T3, T4 tumors, high-grade tumors, extra-parenchymal spread, and certain histological types (undifferentiated carcinoma, squamous cell carcinoma, adenocarcinoma NOS, carcinoma ex-pleomorphic adenoma, and salivary duct carcinoma) • Unresectable disease: Definitive RT, if poor PS palliative RT • Metastatic disease: Palliative radiotherapy or systemic therapy may be considered for symptom control. Metastasectomy may play a role in patients with limited metastases, controlled primary, and non-aggressive histologies in good performance status	
Adjuvant radiotherapy: – No level I or level II evidence to support the use of adjuvant RT. A large number of prospective and retrospective studies are the guidelines for the use of PORT – Indications: T3/T4 cancers, close or positive margins, lymph node metastasis, high or intermediate grade tumors, high-risk histology, adenoid cystic carcinoma, adenocarcinoma, salivary duct carcinoma, high-grade MEC, and carcinoma ex-pleomorphic adenoma, perineural invasion and recurrent tumors. Adjuvant chemoradiation: Clear role not defined, explored in patients with T3–4, or N1–3 disease, intermediate or high-grade tumors, and positive or close ($\leq$1 mm) microscopic margins of resection.	
Follow-up • Regular follow-up as usual for all head-neck malignancies • Follow up every 3–4 months for the first 2 years, every 4–6 months for the next 3 years and annually thereafter • Follow-up should include a thorough clinical examination • Routine CT/MRI scans are not recommended: Imaging for suspected locoregional recurrence	

low-grade adenocarcinomas are well controlled with complete surgical resection, with control reaching 85 percent at 10 years. Adjuvant RT generally is not indicated if adequate margins are obtained. There is no level I or level II evidence to support the use of adjuvant RT. A large number of prospective and retrospective studies are the guidelines for the use of PORT.

Indications are:

- T3/T4 cancers
- Close or positive margins
- Lymph node metastasis
- High- or intermediate-grade tumors
- High-risk histology (adenoid cystic carcinoma, adenocarcinoma, salivary duct carcinoma, high-grade MEC, carcinoma ex-pleomorphic adenoma, perineural invasion, and recurrent tumors)

The optimal adjuvant radiation dose for a malignant salivary gland tumor depends upon the fractionation scheme utilized, but most use doses of 60–66 Gy. The radiation treatment volume encompasses the original tumor bed and regional lymph nodes only if involved or thought to be at high risk. For adenoid cystic carcinoma, neural pathways to the skull base are also included. Conformal RT techniques are preferred.

The role of definitive radical RT is restricted to unresectable tumors. This form of treatment is usually of palliative intent. Fast neutron beam therapy has been shown to be beneficial. However, its use is limited by the extremely scarce availability of fast neutron RT units.

The role of chemotherapy in salivary gland tumors is limited to upfront or recurrent locally advanced inoperable tumors (where the intent is usually palliation rather than cure) and as adjuvant treatment along with radiation ins selected cases. There has been a lot of research with respect to biomarkers and targeted agents designed against the same. This has generated vast amounts of literature that need to be critically analyzed and interpreted before being incorporated into clinical practice.

Concurrent chemoradiation in the adjuvant setting has been offered for the following indications: T3–4, or N1–3 disease, intermediate or high-grade tumors, and positive or close (≤1 mm) margins of resection. In a large retrospective analysis [62] using records from the National Cancer Database (NCDB), patients undergoing chemoradiation were seen to have poorer outcomes than those receiving adjuvant radiation alone. It is to be noted that there was significant heterogeneity between the two groups with reference to adverse prognosticators like histology, grade, and TNM stage, rendering the evidence unreliable. This controversy surrounding the role of adjuvant chemoradiation remains unanswered for now.

Systemic therapy alone is considered in locally advanced incurable tumors or recurrent/progressive advanced tumors for symptom control and palliation. Multiple regimens have been used in salivary gland tumors. In general, response rates are higher in poly chemotherapy regimens as opposed to the single-agent regimen. Selection of chemotherapy should take into consideration the histology and ability to tolerate chemotherapy Staging can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 99–100, Chapter no. 08, Major Salivary Glands, Table: Definition of TNM and AJCC prognostic stage groups which can be accessed at https://emedicine.medscape.com/article/2047666-overview and management in Table 15.

10 Stage-Wise Prognosis with Current RX

10.1 Head and Neck Cancer (Non-nasopharyngeal and HPV −ve Head and Neck Cancer)

Stage	5-Year relative survival (95% CI)
I	69.5–73.5%
II	55.5–60.4%
III	41.8–47.3%
IV	33.6–40.3%

10.2 Nasopharynx

Stage	5-Year relative survival [63]
I	98%
II	92%
III	83%
IV	71%

10.3 Oropharynx (HPV+)

Stage	5-Year relative survival (95% CI) [64]
I	88 (65–91%)
II	81 (77–86%)
III	65 (58–72%)

11 Management of Recurrent Disease Including Specific Palliative Measures

11.1 Nasopharynx

Locoregional failure after initial treatment is seen in approximately 10% of patients. Early detection of loco-regional failure can provide a better chance of salvage. Therefore, regular follow-up of patients is recommended.

PET-CT is superior to CT/MRI in differentiating tumor recurrence from radiation fibrosis. Plasma EBV DNA levels are another useful biomarker for early detection of recurrence, plasma EBV DNA levels may be elevated up to 6 months prior to a clinical recurrence. Recurrent NPC could be treated either by surgical salvage or re-irradiation.

11.1.1 Role of Surgery

Surgery provides good local control with 5-year survival rates ranging between 30% and 50% in recurrent/persistent NPC, especially with early lesions. Surgery also plays a significant role in the treatment of radio-resistant histologies. Surgery is usually performed through open approaches (lateral approach, trans-palatal, mandibular swing, and maxillary approaches) which require translocation of the maxillofacial skeleton or the transposition of critical neurovascular structures. These approaches are associated with significant morbidity especially due to the associated risk of cranial nerve injuries. This has led to the evolution of minimal access, minimally invasive procedures.

Endoscopic endonasal nasopharyngectomy is a feasible minimal access technique indicated for the resection of select recurrent and radio-resistant nasopharyngeal malignancies. It bestows the advantages of lack of external incisions or scars, decreased trauma to adjacent soft tissues and bone, reduced risk of neurological damage, and superior postoperative quality of life.

Chen et al. carried out an endoscopic nasopharyngectomy in 37 recurrent NPC, almost all of them with rT1–T2 tumors. No severe complications or deaths resulting from the operation were observed. The 2-year overall survival rate, local relapse-free survival rate, and progression-free survival rate were 84%, 86%, and 83%, respectively. Robotic-assisted endoscopic nasopharyngeal resection may also play a very important role in these difficult situations.

11.1.2 Role of Re-irradiation

Endocavitary brachytherapy, interstitial brachytherapy, stereotactic radiosurgery, intensity-modulated radiotherapy, and particle beam radiotherapy are various modalities used for re-irradiation in recurrent NPC. A judicious case selection taking into account previous radiation dose, previous radiation volume, interval after previous RT, and current tumor bulk is essential for the success of Re-Irradiation. Promising results are seen, with local control and survival equivalent to nasopharyngectomy in rT1–rT3 lesions. IMRT has emerged as a promising technique of re-irradiation with low complication rates. The complications commonly reported after re-irradiation for NPC include massive epistaxis, nasopharyngeal necrosis, cranial nerve palsies, temporal lobe necrosis, and osteoradionecrosis of the skull base.

11.2 Oral Cavity

Management of recurrences requires a thorough clinical examination and restaging evaluation with PET-CT to rule out metastatic disease. Patients with good performance status, resectable small-volume recurrences, and long disease-free intervals are most likely to benefit from salvage treatment. Salvage surgery is the best option if feasible and should be followed up by Re-irradiation if indicated and possible as it is shown to improve DFS [65]. Unresectable recurrences may be considered for re-irradiation; however, outcomes are not favorable.

11.3 Oropharynx

PET-CT should be performed in recurrent cases to rule out metastatic disease. For resectable recurrences, salvage surgery should be performed followed by re-irradiation if feasible. Unresectable recurrences should be treated with re-irradiation if possible, if surgery or re-irradiation is not possible systemic therapy may be considered.

11.4 Larynx and Hypopharynx

For resectable recurrences after previous surgery or radiotherapy, salvage surgery should be performed followed by chemo-radiation or re-irradiation (depending on if previ-

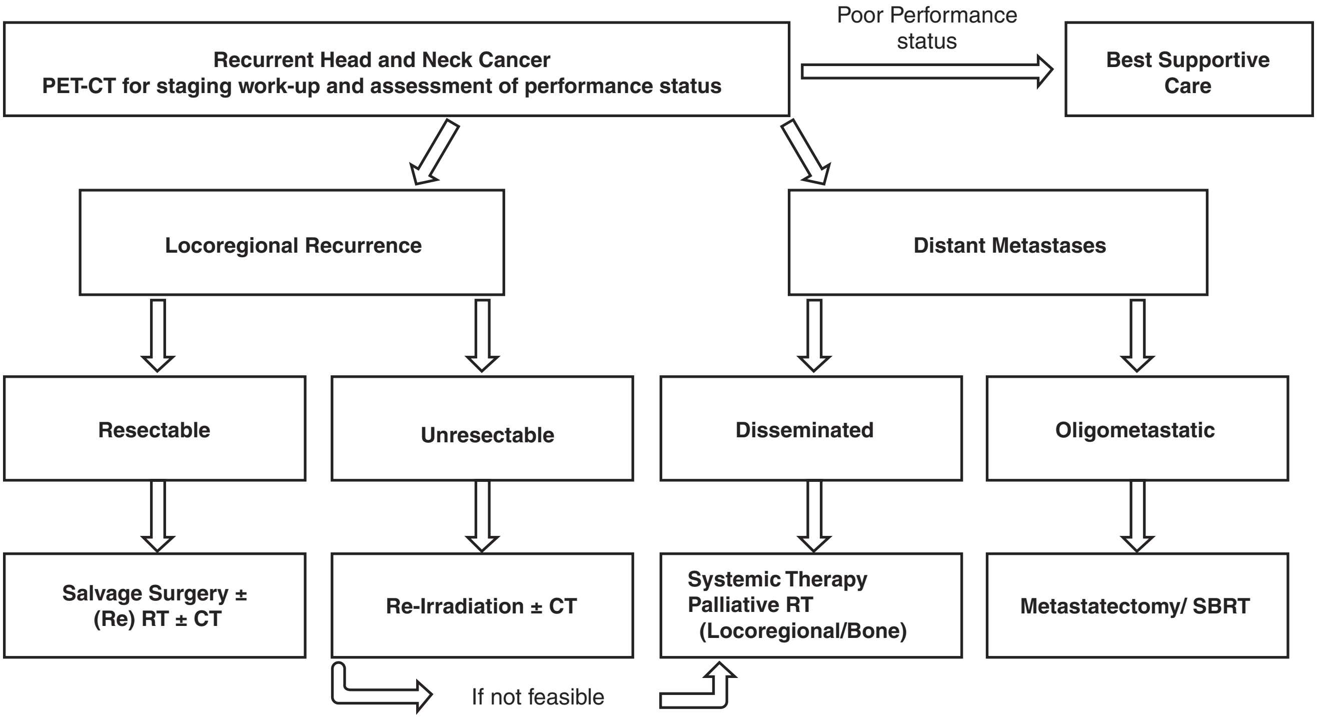

Recurrent Head and Neck Cancer
PET-CT for staging work-up and assessment of performance status
Poor Performance status
Best Supportive Care
Locoregional Recurrence
Distant Metastases
Resectable
Unresectable
Disseminated
Oligometastatic
Salvage Surgery ± (Re) RT ± CT
Re-Irradiation ± CT
Systemic Therapy
Palliative RT
(Locoregional/Bone)
Metastatectomy/ SBRT
If not feasible

Fig. 2 Management algorithm for recurrent HNC

ously irradiated or not). Unresectable recurrences are treated with chemo-radiation (if not previously irradiated) or re-irradiation if possible, if surgery or Re-irradiation is not possible systemic therapy may be considered. If in poor general condition then Palliative radiation/chemotherapy or BSC as tolerated to achieve the best symptomatic control.

11.5 Nasal Cavity and Paranasal Sinuses

Resectable recurrences: Salvage surgery followed by re-irradiation if feasible.

Unresectable recurrences: Chemo-radiation (if not previously irradiated) or re-irradiation if possible, if surgery or Re-irradiation is not possible systemic therapy may be considered.

11.6 Salivary Gland Tumors

Resectable recurrences: Surgery is preferred, surgery in these situations has a high risk for facial nerve damage.

Unresectable recurrences: Irradiation should be considered.

If neither surgery nor irradiation is feasible (e.g., previously irradiated), systemic chemotherapy may be considered.

Figure 2 presents a management algorithm for recurrent HNC.

12 How We Do It at TMC (Figs. 3, 4, 5, 6, 7, and 8)

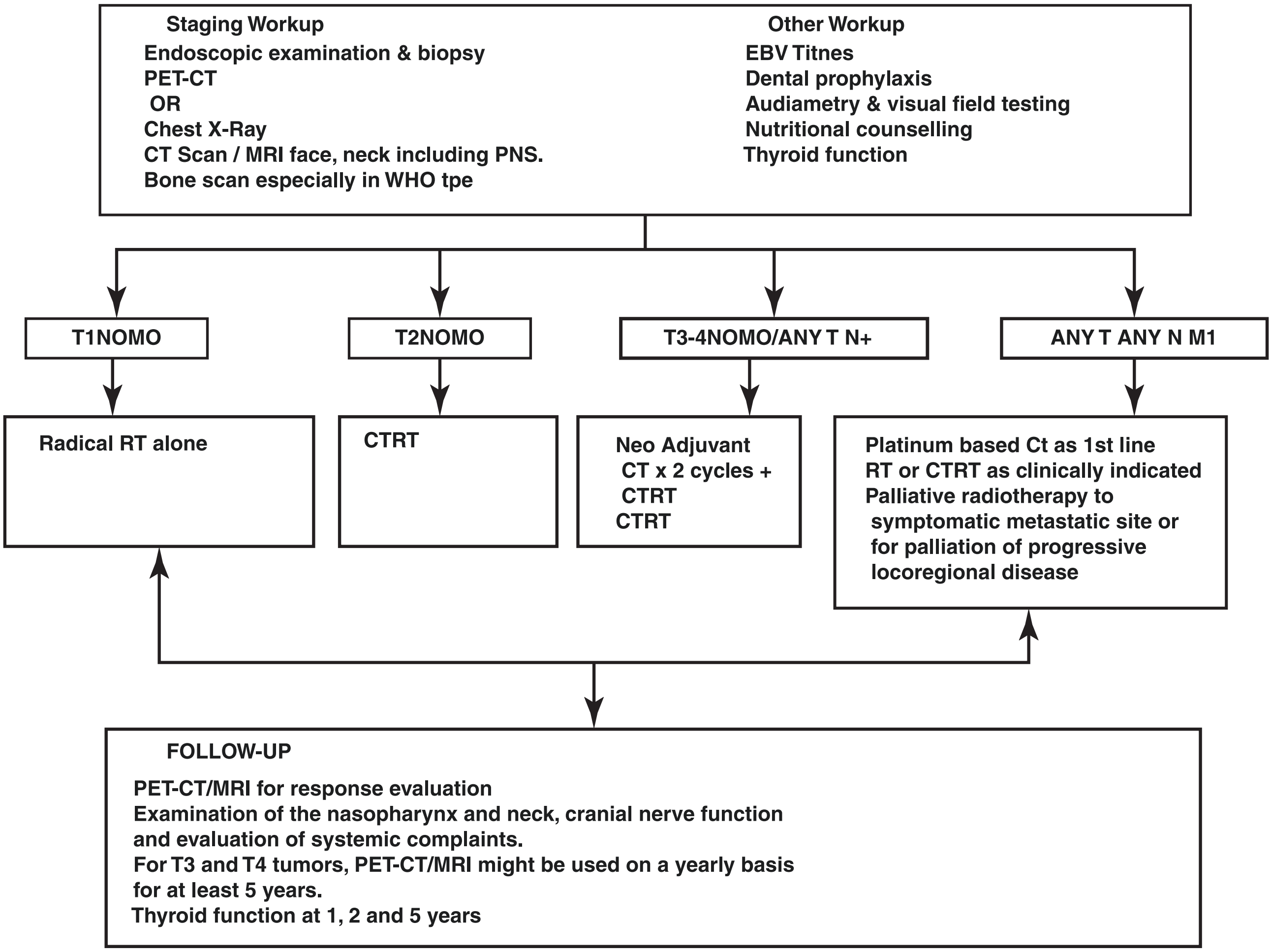
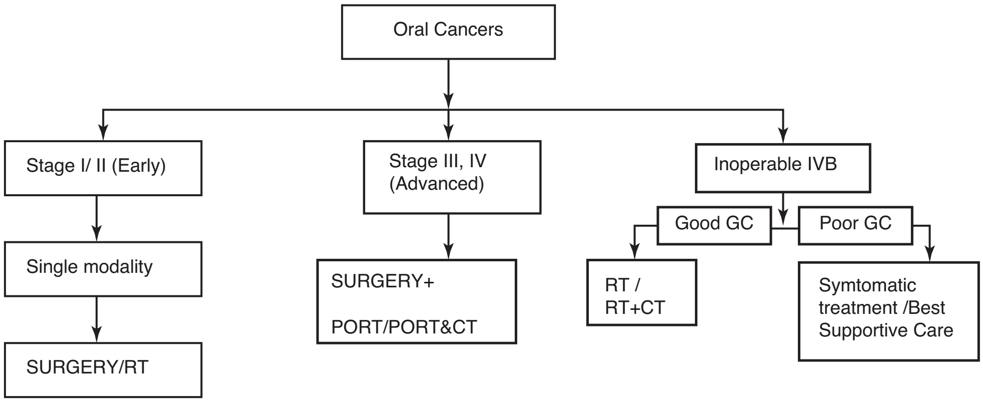

Staging Workup
Endoscopic examination & biopsy
PET-CT
OR
Chest X-Ray
CT Scan / MRI face, neck including PNS.
Bone scan especially in WHO tpe
Other Workup
EBV Titnes
Dental prophylaxis
Audiametry & visual field testing
Nutritional counselling
Thyroid function
T1NOMO
T2NOMO
T3-4NOMO/ANY T N+
ANY T ANY N M1
Radical RT alone
CTRT
Neo Adjuvant
CT x 2 cycles +
CTRT
CTRT
Platinum based Ct as 1st line
RT or CTRT as clinically indicated
Palliative radiotherapy to
symptomatic metastatic site or
for palliation of progressive
locoregional disease
FOLLOW-UP
PET-CT/MRI for response evaluation
Examination of the nasopharynx and neck, cranial nerve function
and evaluation of systemic complaints.
For T3 and T4 tumors, PET-CT/MRI might be used on a yearly basis
for at least 5 years.
Thyroid function at 1, 2 and 5 years

Fig. 3 Nasopharynx

Fig. 4 Oral cavity


Oral Cancers
Stage I/ II (Early)
Stage III, IV
(Advanced)
Inoperable IVB
Good GC
Poor GC
Single modality
SURGERY/RT
SURGERY+
PORT/PORT&CT
RT /
RT+CT
Symtomatic
treatment /Best
Supportive Care

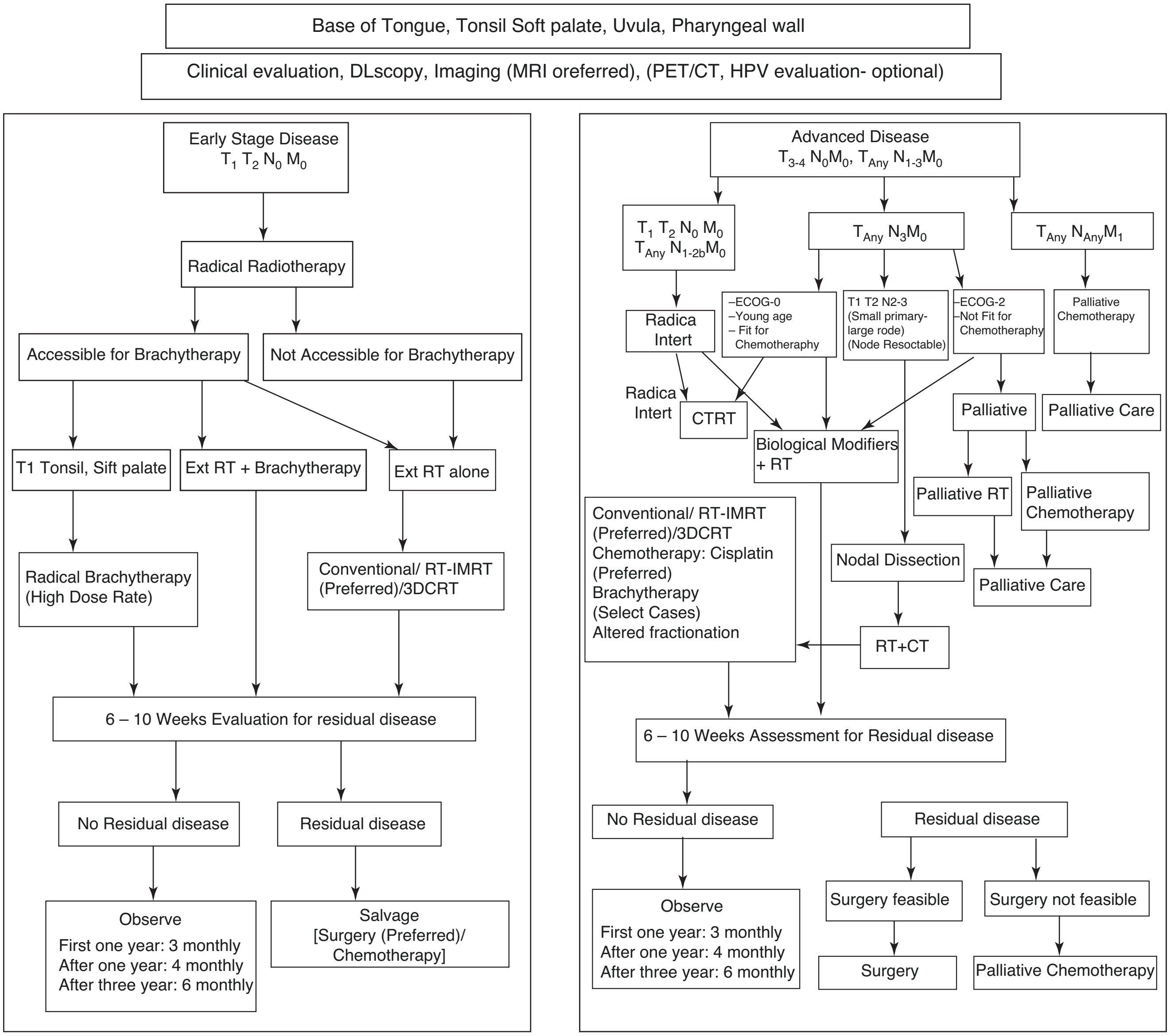
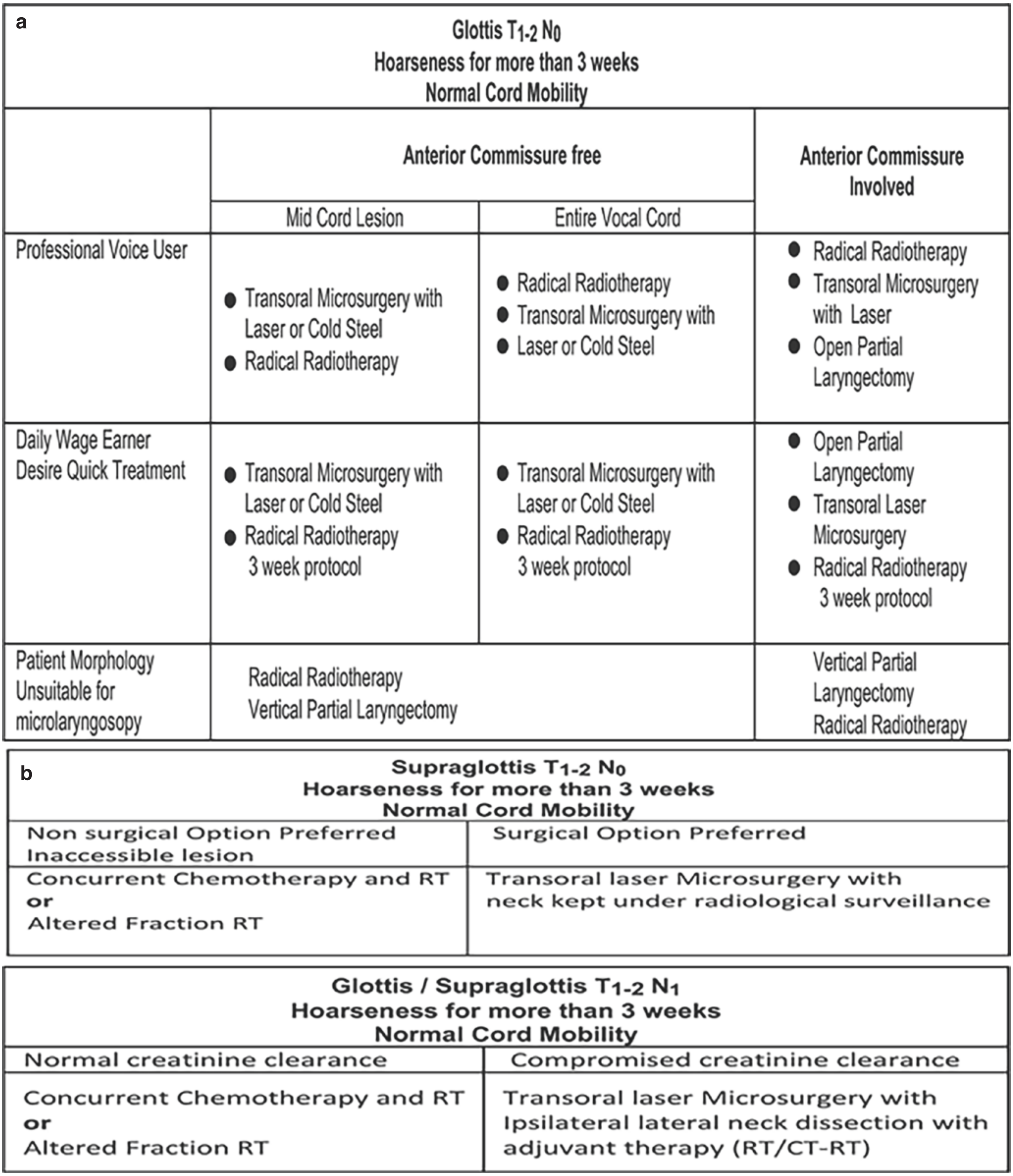

Base of Tongue, Tonsil Soft palate, Uvula, Pharyngeal wall
Clinical evaluation, DLscopy, Imaging (MRI oreferred), (PET/CT, HPV evaluation- optional)
Early Stage Disease T_1 T_2 N_0 M_0
Radical Radiotherapy
Accessible for Brachytherapy
Not Accessible for Brachytherapy
T1 Tonsil, Sift palate
Ext RT + Brachytherapy
Ext RT alone
Radical Brachytherapy (High Dose Rate)
Conventional/ RT-IMRT (Preferred)/3DCRT
6 – 10 Weeks Evaluation for residual disease
No Residual disease
Residual disease
Observe
First one year: 3 monthly
After one year: 4 monthly
After three year: 6 monthly
Salvage [Surgery (Preferred)/ Chemotherapy]
Advanced Disease $T_{3\text{-}4}$ N_0M_0, T_{Any} $N_{1\text{-}3}M_0$
T_1 T_2 N_0 M_0 T_{Any} $N_{1\text{-}2b}M_0$
T_{Any} N_3M_0
T_{Any} $N_{Any}M_1$
Radica Intert
–ECOG-0 –Young age – Fit for Chemotheraphy
T1 T2 N2-3 (Small primary- large rode) (Node Resoctable)
–ECOG-2 –Not Fit for Chemotheraphy
Palliative Chemotherapy
Radica Intert
CTRT
Biological Modifiers + RT
Palliative
Palliative Care
Palliative RT
Palliative Chemotherapy
Conventional/ RT-IMRT (Preferred)/3DCRT Chemotherapy: Cisplatin (Preferred) Brachytherapy (Select Cases) Altered fractionation
Nodal Dissection
Palliative Care
RT+CT
6 – 10 Weeks Assessment for Residual disease
No Residual disease
Residual disease
Surgery feasible
Surgery not feasible
Observe
First one year: 3 monthly
After one year: 4 monthly
After three year: 6 monthly
Surgery
Palliative Chemotherapy

Fig. 5 Oropharynx



a

Glottis $T_{1\text{-}2}$ N_0
Hoarseness for more than 3 weeks
Normal Cord Mobility

	Anterior Commissure free		**Anterior Commissure Involved**
	Mid Cord Lesion	Entire Vocal Cord	
Professional Voice User	● Transoral Microsurgery with Laser or Cold Steel ● Radical Radiotherapy	● Radical Radiotherapy ● Transoral Microsurgery with ● Laser or Cold Steel	● Radical Radiotherapy ● Transoral Microsurgery with Laser ● Open Partial Laryngectomy
Daily Wage Earner Desire Quick Treatment	● Transoral Microsurgery with Laser or Cold Steel ● Radical Radiotherapy 3 week protocol	● Transoral Microsurgery with Laser or Cold Steel ● Radical Radiotherapy 3 week protocol	● Open Partial Laryngectomy ● Transoral Laser Microsurgery ● Radical Radiotherapy 3 week protocol
Patient Morphology Unsuitable for microlaryngosopy	Radical Radiotherapy Vertical Partial Laryngectomy		Vertical Partial Laryngectomy Radical Radiotherapy

b

Supraglottis $T_{1\text{-}2}$ N_0
Hoarseness for more than 3 weeks
Normal Cord Mobility

Non surgical Option Preferred Inaccessible lesion	Surgical Option Preferred
Concurrent Chemotherapy and RT or Altered Fraction RT	Transoral laser Microsurgery with neck kept under radiological surveillance

Glottis / Supraglottis $T_{1\text{-}2}$ N_1
Hoarseness for more than 3 weeks
Normal Cord Mobility

Normal creatinine clearance	Compromised creatinine clearance
Concurrent Chemotherapy and RT or Altered Fraction RT	Transoral laser Microsurgery with Ipsilateral lateral neck dissection with adjuvant therapy (RT/CT-RT)

Fig. 6 (**a**–**e**) Larynx and hypopharynx

c

Glottis / Supraglottis T_{1-2} N_{2-3}
Hoarseness for more than 3 weeks
Normal Cord Mobility

Non Surgical Option		Surgical Option for Primary	Split Therapy
Normal creatinine clearance	Compromised creatinine clearance and performance status		
Concurrent Chemotherapy and RT	Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT	● Transoral Laser Microsurgery with bilateral lateral neck dissection with adjuvant therapy (RT/CT-RT) ● Open Partial laryngectomy* with bilateral lateral neck dissection with adjuvant adjuvant therapy (RT/CT-RT)	Neck Dissection with adjuvant adjuvant therapy (RT/CT-RT)

* Vertical Partial Laryngectomy for Glottic growth / Supraglottic Laryngectomy for Supraglottic growth

Glottis / Supraglottis T3 Any N
Hoarseness Impaired Cord Mobility / Fixed cord
CT SCAN Larynx – Paraglottic Space /Pre-epiglottic Space Involvement
Operable Neck nodes

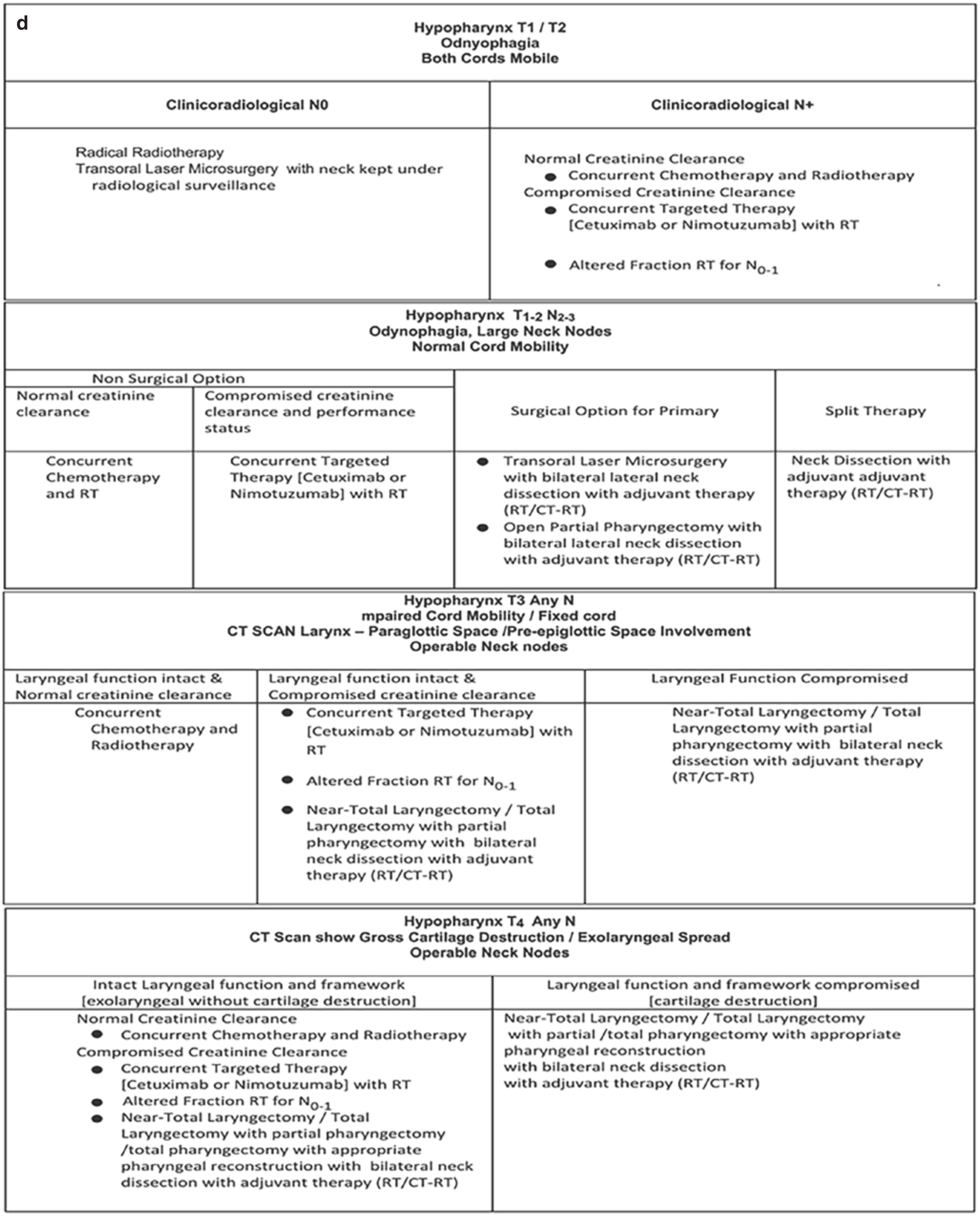
Laryngeal function intact & Normal creatinine clearance	Laryngeal function intact & Compromised creatinine clearance	Laryngeal Function Compromised
Concurrent Chemotherapy and Radiotherapy	● Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT ● Altered Fraction RT for N_{0-1} ● Open Partial Laryngectomy* with Ipsilateral for [N0] / bilateral for [N+] neck dissection with adjuvant therapy (RT/CT-RT)	Near-Total Laryngectomy / Total Laryngectomy with bilateral lateral neck dissection with adjuvant therapy (RT/CT-RT)

*Supracricoid Laryngectomy for Glottic growth / Supraglottic Laryngectomy for Supraglottic growth

Glottis / SupraglottisT_4 Any N
CT Scan show Gross Cartilage Destruction / Exolaryngeal Spread
Operable Neck Nodes

Intact Laryngeal function and framework [exolaryngeal without cartilage destruction]	Laryngeal function and framework compromised [cartilage destruction]
Normal Creatinine Clearance ● Concurrent Chemotherapy and Radiotherapy Near-Total Laryngectomy / Total Laryngectomy with bilateral lateral neck dissection with adjuvant therapy (RT/CT-RT) Compromised Creatinine Clearance ● Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT ● Altered Fraction RT for N_{0-1} ● Near-Total Laryngectomy / Total Laryngectomy with bilateral lateral neck dissection with adjuvant therapy (RT/CT-RT)	Near-Total Laryngectomy / Total Laryngectomy with bilateral lateral neck dissection with adjuvant therapy (RT/CT-RT)

Fig. 6 (continued)



d

Hypopharynx T1 / T2
Odnyophagia
Both Cords Mobile

Clinicoradiological N0	**Clinicoradiological N+**
Radical Radiotherapy Transoral Laser Microsurgery with neck kept under radiological surveillance	Normal Creatinine Clearance ● Concurrent Chemotherapy and Radiotherapy Compromised Creatinine Clearance ● Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT ● Altered Fraction RT for N_{0-1}

Hypopharynx T_{1-2} N_{2-3}
Odynophagia, Large Neck Nodes
Normal Cord Mobility

Non Surgical Option		Surgical Option for Primary	Split Therapy
Normal creatinine clearance	Compromised creatinine clearance and performance status		
Concurrent Chemotherapy and RT	Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT	● Transoral Laser Microsurgery with bilateral lateral neck dissection with adjuvant therapy (RT/CT-RT) ● Open Partial Pharyngectomy with bilateral lateral neck dissection with adjuvant therapy (RT/CT-RT)	Neck Dissection with adjuvant adjuvant therapy (RT/CT-RT)

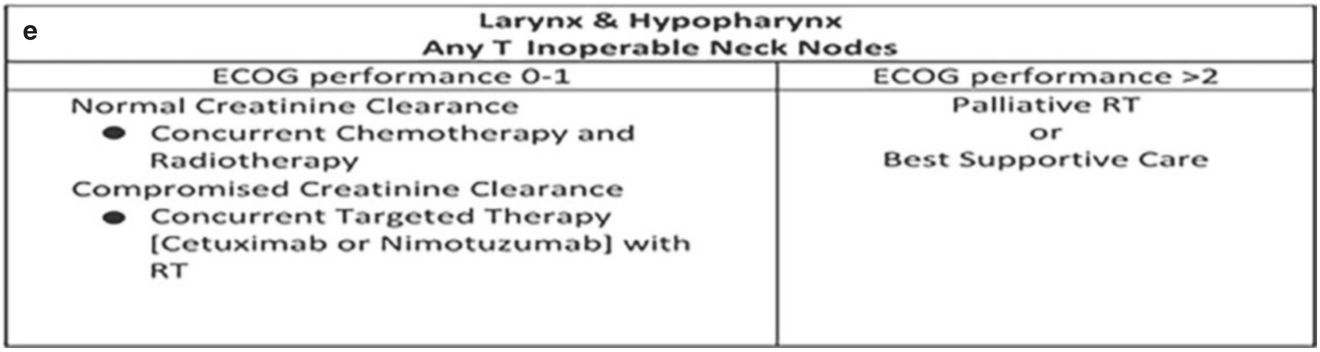
Hypopharynx T3 Any N
mpaired Cord Mobility / Fixed cord
CT SCAN Larynx – Paraglottic Space /Pre-epiglottic Space Involvement
Operable Neck nodes

Laryngeal function intact & Normal creatinine clearance	Laryngeal function intact & Compromised creatinine clearance	Laryngeal Function Compromised
Concurrent Chemotherapy and Radiotherapy	● Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT ● Altered Fraction RT for N_{0-1} ● Near-Total Laryngectomy / Total Laryngectomy with partial pharyngectomy with bilateral neck dissection with adjuvant therapy (RT/CT-RT)	Near-Total Laryngectomy / Total Laryngectomy with partial pharyngectomy with bilateral neck dissection with adjuvant therapy (RT/CT-RT)

Hypopharynx T_4 Any N
CT Scan show Gross Cartilage Destruction / Exolaryngeal Spread
Operable Neck Nodes

Intact Laryngeal function and framework [exolaryngeal without cartilage destruction]	Laryngeal function and framework compromised [cartilage destruction]
Normal Creatinine Clearance ● Concurrent Chemotherapy and Radiotherapy Compromised Creatinine Clearance ● Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT ● Altered Fraction RT for N_{0-1} ● Near-Total Laryngectomy / Total Laryngectomy with partial pharyngectomy /total pharyngectomy with appropriate pharyngeal reconstruction with bilateral neck dissection with adjuvant therapy (RT/CT-RT)	Near-Total Laryngectomy / Total Laryngectomy with partial /total pharyngectomy with appropriate pharyngeal reconstruction with bilateral neck dissection with adjuvant therapy (RT/CT-RT)

Fig. 6 (continued)



e

Larynx & Hypopharynx
Any T Inoperable Neck Nodes

ECOG performance 0-1	ECOG performance >2
Normal Creatinine Clearance ● Concurrent Chemotherapy and Radiotherapy Compromised Creatinine Clearance ● Concurrent Targeted Therapy [Cetuximab or Nimotuzumab] with RT	Palliative RT or Best Supportive Care

Fig. 30.6 (continued)

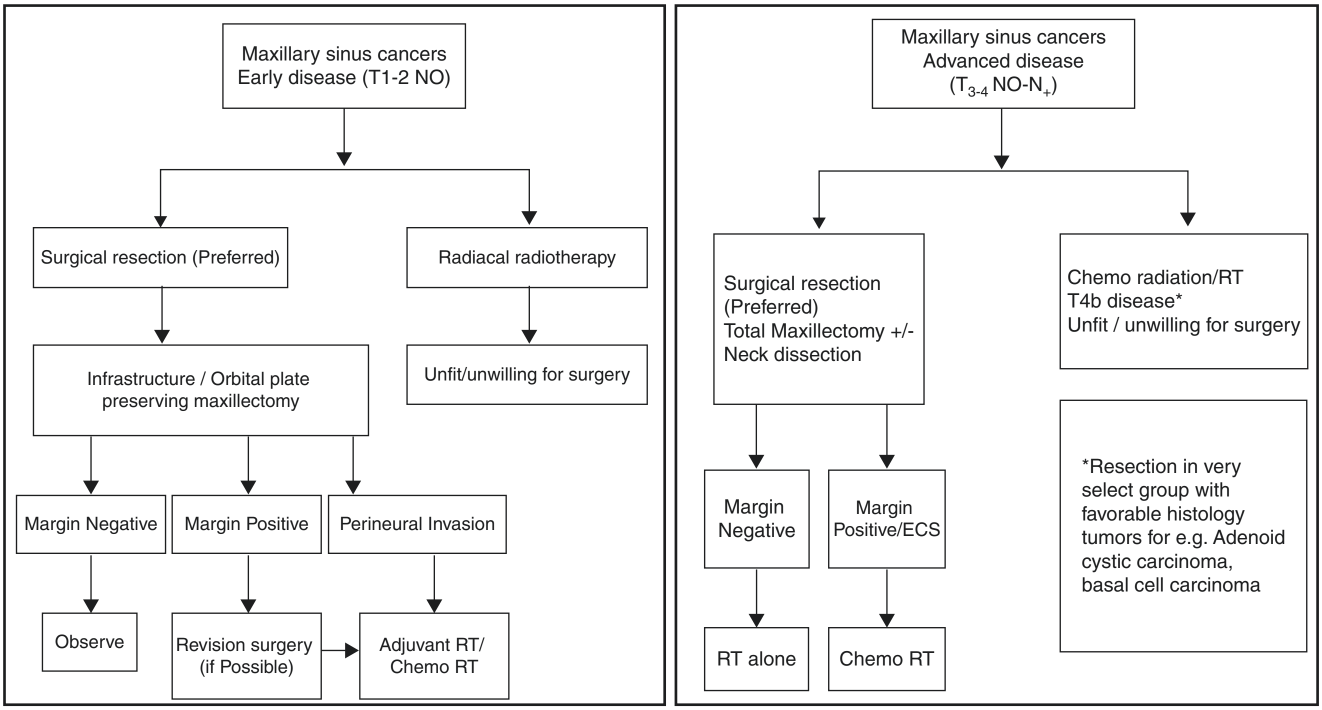

Maxillary sinus cancers
Early disease (T1-2 NO)
Surgical resection (Preferred)
Radiacal radiotherapy
Infrastructure / Orbital plate preserving maxillectomy
Unfit/unwilling for surgery
Margin Negative
Margin Positive
Perineural Invasion
Observe
Revision surgery (if Possible)
Adjuvant RT/ Chemo RT
Maxillary sinus cancers
Advanced disease
(T3-4 NO-N+)
Surgical resection (Preferred) Total Maxillectomy +/- Neck dissection
Chemo radiation/RT
T4b disease*
Unfit / unwilling for surgery
Margin Negative
Margin Positive/ECS
*Resection in very select group with favorable histology tumors for e.g. Adenoid cystic carcinoma, basal cell carcinoma
RT alone
Chemo RT

Fig. 7 Paranasal sinuses

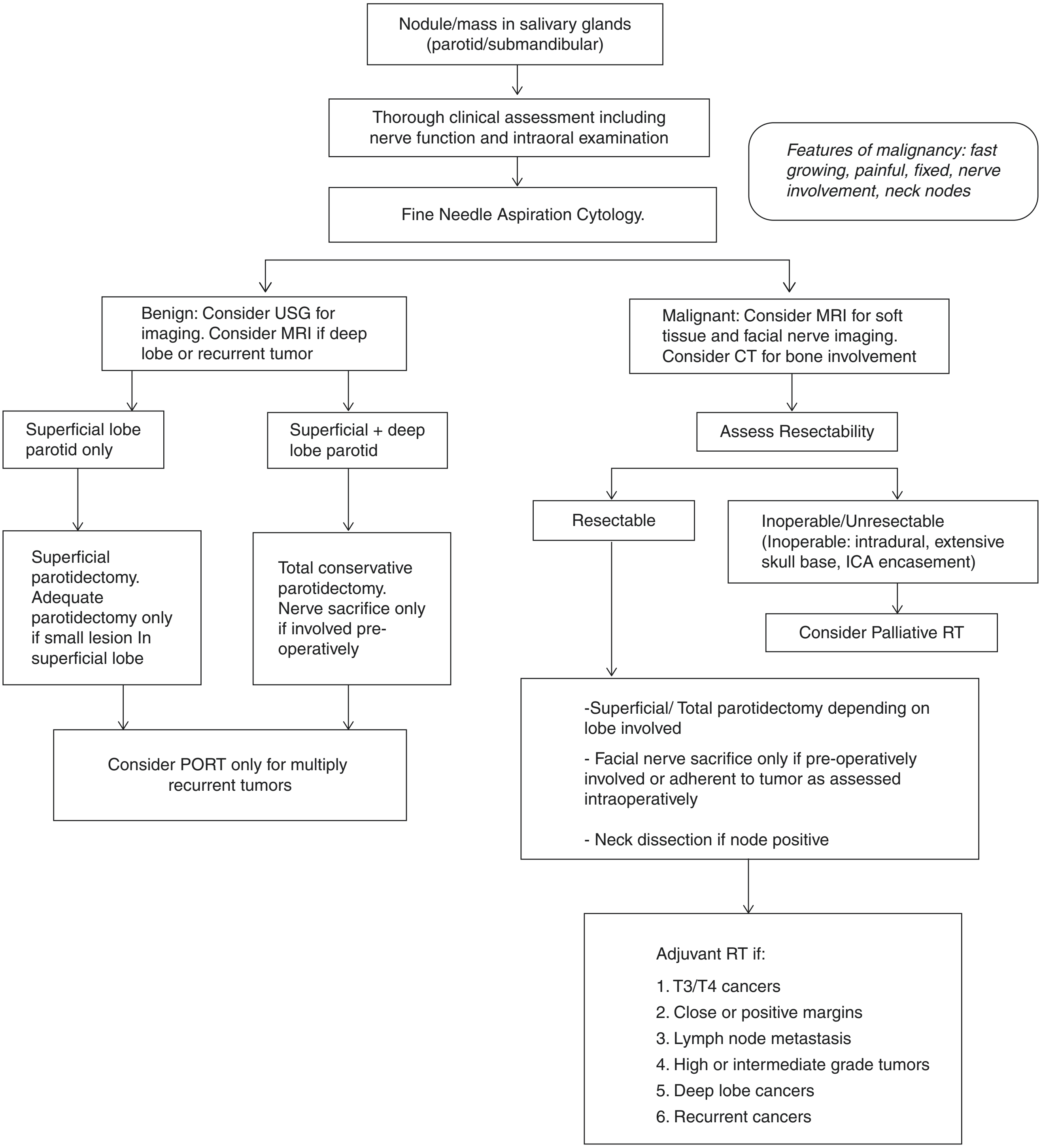

Nodule/mass in salivary glands (parotid/submandibular)
Thorough clinical assessment including nerve function and intraoral examination
Features of malignancy: fast growing, painful, fixed, nerve involvement, neck nodes
Fine Needle Aspiration Cytology.
Benign: Consider USG for imaging. Consider MRI if deep lobe or recurrent tumor
Malignant: Consider MRI for soft tissue and facial nerve imaging. Consider CT for bone involvement
Superficial lobe parotid only
Superficial + deep lobe parotid
Assess Resectability
Resectable
Inoperable/Unresectable (Inoperable: intradural, extensive skull base, ICA encasement)
Consider Palliative RT
Superficial parotidectomy. Adequate parotidectomy only if small lesion In superficial lobe
Total conservative parotidectomy. Nerve sacrifice only if involved pre-operatively
-Superficial/ Total parotidectomy depending on lobe involved
- Facial nerve sacrifice only if pre-operatively involved or adherent to tumor as assessed intraoperatively
- Neck dissection if node positive
Consider PORT only for multiply recurrent tumors
Adjuvant RT if:
1. T3/T4 cancers
2. Close or positive margins
3. Lymph node metastasis
4. High or intermediate grade tumors
5. Deep lobe cancers
6. Recurrent cancers

Fig. 8 Salivary gland tumors

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Thyroid and Parathyroid Cancers

Richa Vaish and Anil K. D’Cruz

Abbreviations

ATA	American Thyroid Association
CEA	Carcinoembryonic antigen
CECT	Contrast-enhanced computed tomography
EBRT	External beam radiotherapy
FCDC	Follicular cell-derived carcinoma
FNAC	Fine-needle aspiration cytology
HPJT	Hyperparathyroidism jaw-tumor syndrome
MEN	Multiple endocrine neoplasia
MRI	Magnetic resonance imaging
MTC	Medullary thyroid cancer
PDGFR	Platelet-derived growth factor receptor
PET	Positron emission tomography
PTH	Parathyroid hormone
RCT	Randomized-controlled trial
ROM	Risk of malignancy
RT	Radiotherapy
TIRADS	Thyroid Imaging Reporting and Data Systems
TKI	Tyrosine kinase inhibitors
TMC RSS	Thyroid multimodal-imaging comprehensive risk stratification scoring
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
WHO	World Health Organization

1 Introduction

Thyroid cancers are the most common endocrine malignancy that is either follicular cell-derived (FCDC), arising from the parafollicular C cells of neuroendocrine origin which are the medullary thyroid cancers (MTC) or anaplastic. FCDC account for 90% of all thyroid malignancies and are of four types—papillary (most common), follicular, Hurthle cell and poorly differentiated thyroid cancers. These vary in biological aggressiveness from well-differentiated to the poorly differentiated cancers. World Health Organization (WHO) classifies Hurthle cell carcinoma a separate entity and not a variant of follicular carcinoma due to their peculiar behavior [1]. Papillary thyroid cancer has several variants namely papillary microcarcinoma, encapsulated, the follicular and cribriform morular variant which have an excellent prognosis; high-risk variants like diffuse sclerosing, tall cell, columnar cell, hobnail, oncocytic and solid/trabecular variant and others like spindle cell, clear cell and Warthin-like which are extremely rare and their clinical behavior is poorly understood [2]. Majority of these cancers are sporadic with <5% being hereditary in origin.

2 Incidence and Epidemiology

Globocan data report the age-standardized rate (ASR) of 6.7 per 100,000 people with 567,233 being diagnosed worldwide annually. The incidence is lower in India with ASR of 1.4 per 100,000 people and 18,688 new cases being reported every year [3]. Vecchia et al. observing the incidence and mortality trends over four decades noted a significant rise in the incidence of thyroid tumors particularly papillary thyroid cancer (PTC) with a stable decrease in mortality during this time period. The mortality has declined with an annual percentage change of −2/−3% in men and −2/−5% in women in most major countries of the world. This incongruity between the incidence and mortality has been attributed to overdiagnosis which is secondary to the increased use of

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imaging [4]. These tumors are usually small and are diagnosed in the preclinical stage which would have stayed unnoticed in all probability in the lifespan of the individual [5, 6]. Others have argued that in addition to this apparent increase due to over diagnosis, there is a true increase in incidence. This stems from the fact that the rise in incidence is observed not only for small tumors but also for tumor with high volume and across all stages. Lim et al. observed the trends of thyroid cancer mortality and incidence from the Surveillance, Epidemiology and End Results-9 (SEER-9) data. There was an average 3.6% increase in the incidence of thyroid cancers annually which was primarily related to PTC. The increase per year was 4.6%, 4.3% and 2.4% for localized, regional and distant disease respectively for PTC [7]. Also, the increase is more in females compared to males and in specific birth cohorts. The increase has been attributed to environmental carcinogens and medical radiation [8].

3 Differentiated Thyroid Cancers

3.1 Clinical Presentation

Thyroid cancers present as a solitary nodule in the majority of cases while the remaining present as multiple nodules or diffuse enlargement of the gland. Well-differentiated thyroid cancers affect females about 3 to 4 times more than males. PTC presents with small thyroid nodules less than 2 cm in size and is early staged in more than 80% in the western world, as mentioned earlier attributed to increased screening/imaging [8]. These tumors can be multifocal in as high as 60% in papillary microcarcinoma [9]. The prevalence of regional and distant metastasis at the time of presentation is about 20% and 2%, respectively. However, the true initial prevalence based on the histopathology and I-131 therapeutic whole-body scans is higher with 30% regional and 10% distant metastasis [10]. Papillary thyroid cancer is characterized by a lymphatic spread with a high incidence of nodal metastasis whereas follicular carcinoma has the predilection for hematogenous spread. About 10% to 15% of follicular carcinoma can have distant metastasis at the time of presentation. The incidence of distant metastasis rises to as high as 34% during the course of the disease, particularly in Hurthle cell carcinomas [11]. Distant metastasis is synchronous in 40% to 55% with the most common site being lung (43–49%) followed by bone (24–33%) [12–14]. Metachronous distant metastasis (occurring >12 months after the initial diagnosis) occurs in 45% and have poorer survival compared to synchronous metastasis [14]. The extrathyroidal extension (ETE) is seen in 10% to 32% of cases and the decreasing order of occurrence involves strap muscles, recurrent laryngeal nerve (RLN) and trachea [11, 15]. Thyroid cancer is the only site in the body where age is an important prognostic factor [16]. The tumor size and regional metastasis increase are seen at extreme ages. The features of biological aggressiveness including capsular invasion, extrathyroidal extension and neural or vascular invasion are more frequent in the younger population [17]. Despite these features of pediatric DTC, the survival outcomes of the children and young adult are the same [18]. Locally advanced thyroid cancers may present with the symptoms of hoarseness and aspiration with RLN involvement and resultant vocal cord fixation. Stridor or hemoptysis indicates laryngotracheal invasion. Gross ETE may cause infiltration of the upper aerodigestive tract and deviation of the larynx and trachea.

3.2 Evaluation and Work-Up

Thyroid function test (T3/T4/thyroid-stimulating hormone [TSH]) is the first test ordered in the workup of any thyroid nodule. Thyroid cancer with hyperthyroidism is an exception rather than a rule and mandates a radionuclide scan (iodine-123 or technetium 99mTc pertechnetate) to assess for the presence of hyperfunctioning nodule which almost always denotes benignity. However, a nonfunctioning cold nodule should be investigated further as the risk of malignancy in these nodules is high ranging from 5% to 15% [19]. Thyroid cancer usually arises in the background of a euthyroid status sometimes with a raised TSH. Gross hypothyroidism is usually a medical condition.

Given the high incidence of thyroid nodules in the general population and the presence of occult microcarcinoma, a diagnostic workup is recommended only for nodules >1 cm to avoid overtreatment of cancers that are probably incidental and would never manifest in the lifetime of a patient. In the case of multinodular goiters (MNG), size of 2 cm is suggested as the cut-off for further investigation by the American Thyroid Association (ATA) [20]. This is important as MNGs are common in our part of the world. High-risk nodules viz. those diagnosed incidentally on PET scans for other causes, nodules in children, a family history of thyroid cancer and those with a prior history of exposure to radiotherapy in childhood are investigated irrespective of nodule size given the high likelihood of harboring a malignancy.

DTC is associated with reliable tumor markers namely thyroglobulin. However, its role is limited as a diagnostic or baseline screening tool. Thyroglobulin has low sensitivity and specificity with the thyroid gland in-situ as it is raised in other conditions as well (thyroiditis, benign goiters, etc.). The main role of these markers is in the follow-up of patients for early detection of disease recurrence.

Locally advanced presentation with the invasion of surrounding structures is seen in 13% to 15% of thyroid cancers which most commonly involved straps followed by RLN [21]. It must be kept in mind that only a third of these patients

Table 1 Bethesda system for reporting thyroid cytopathology: risk of malignancy

Bethesda category	Risk of malignancy (%) [98]	Re-estimated risk of malignancy[a] (%) [99]	Suggested management
Nondiagnostic or unsatisfactory (Bethesda I)	1–4	5–10	Repeat FNAC under USG guidance
Benign (Bethesda II)	0–3	0–3	Observe if surgery not warranted for cosmesis, size/pressure
Atypia of undetermined significance or follicular lesion of undetermined significance (Bethesda III)	5–15	6–18	Observe[b]/diagnostic lobectomy/ molecular markers
Follicular neoplasm or suspicious for a follicular neoplasm (Bethesda IV)	15–30	10–40	Observe[b]/diagnostic lobectomy/ molecular marker
Suspicious for malignancy (Bethesda V)	60–75	45–60	Diagnostic lobectomy
Malignant (Bethesda VI)	97–99	94–96	Therapeutic hemi/total thyroidectomy

[a] Risk estimation considering NIFTP as nonmalignant

[b] If nodule size is small, no high-risk factor on history or clinical examination, no high-risk radiological features

present with a change in voice [11]. Fiber optic laryngoscopy should be performed in every case and function of the cord should be documented both to alert the clinician of possible nerve involvement as well as for medicolegal issues. Laryngotracheal framework infiltration should be confirmed on endoscopy if suspected following imaging.

Ultrasonography (USG) is the initial imaging of choice given its multiplanar capability, easy availability, affordability and the lack of radiation exposure. It helps to assess the echogenicity, size, location, tumor and gland interface and characterizes the tumor as cystic or solid. High-risk features suggestive of malignancy are a solid hypoechoic nodule, presence of microcalcification, micro lobulations or irregular margins and a nodule that is taller than wide. These five high-risk features form the basis of the TIRADS (Thyroid Imaging Reporting and Data Systems) which is a diagnostic classification used to estimate the risk of malignancy (ROM) in the thyroid nodules [22]. The biggest disadvantage of sonography is that it is highly operator dependent. Besides, the sensitivity to detect nodal metastasis in the central compartment is low. Nodes in the retro/parapharyngeal region and mediastinum are also not visualized on sonography. Addition of cross-sectional imaging improves the sensitivity in detecting these nodal metastases both in the central and lateral compartment.

Cross-sectional imaging is needed in cases with locally advanced cancer to accurately assess the extent of disease. Contrast-enhanced computed tomography (CECT) is the imaging modality of choice when laryngotracheal framework involvement is suspected. Magnetic resonance imaging (MRI) and endoscopic ultrasound have higher sensitivity in evaluating esophageal involvement.

Fine-needle aspiration cytology (FNAC) is performed to establish the diagnosis. It is preferably performed under the US guidance particularly when the tumor is small or posteriorly located. The ideal cytology smear targets at obtaining at least 5–6 follicular cell groups with each group having 10–15 cells preferably on single slide [23]. FNAC reporting is now standardized with various reporting systems described in the literature. The Bethesda system is most widely adopted and is used to estimate the ROM classified under six categories. The recent recognition of well-differentiated tumors of uncertain malignant potential/noninvasive follicular thyroid neoplasm with papillary-like nuclear features has led to a recalibration of the Bethesda system of classification (Table 1). While the accuracy of FNAC for diagnosing PTC is high it has limited utility in establishing the diagnosis of follicular and Hurthle carcinoma given that capsular and vascular invasion, the essential prerequisites of malignancy cannot be demonstrated by FNAC. This, therefore, results in about 25% of the FNAC's being reported as indeterminate on the Bethesda system. While guidelines recommend considering molecular profiling in these cases it has not translated into the incorporation in routine practice. The main reasons are high costs, relative lack of availability and results that have not been corroborated in real-world practice. Moreover, the majority of these nodules turn out to be benign or are indolent cancers on final histopathology with no real detriment to survival had the patient been on active surveillance. A pragmatic approach, therefore, would be to use these tests when the clinicoradiological findings reveal high-risk features which would prompt the clinician to a diagnostic lobectomy. These tests can be useful in this cohort to help avoid surgery. However, it should be kept in mind that the negative predictive value (NPV) of these tests in such a scenario may be lower than what has been reported in the literature [24, 25].

3.3 Principles of Management

Surgery is the mainstay of treatment for thyroid cancers. Close to 90% of thyroid cancers are differentiated and have an excellent prognosis and low mortality in the majority. Therefore, the aim of the management of these cancers is complete surgical clearance of disease while avoiding treatment-related morbidity. The RLN damage can occur in

0.5% to 3% of patients, while hypoparathyroidism (temporary/permanent) has been reported in as high as 20% of patients even in the most experienced hands [26]. Surgery must therefore be adequate with the gross clearance of disease. Overzealous clearance does not offer survival benefit but increases the risk of hypoparathyroidism and RLN injury, on the other hand, inadequate surgery increases the risk of recurrence and resurgery is associated with higher morbidity. Given the unpredictable and relatively high rates of complications following surgery and the fact that thyroid occult papillary microcarcinomas are common in a significant proportion of the general population, there is a school of thought that advocates observation in select cases with microcarcinomas. The ideal patient for this approach must have a purely intraparenchymal tumor, preferably not posteriorly located (where there is a risk of RLN fixation) and without nodal metastasis. Surgery is recommended only in case of disease progression, i.e., increase in nodule size or the appearance of metastatic nodes. This approach of surveillance was first shown to be safe from large series from Japan and subsequently by others as well [27, 28].

3.3.1 Surgical Management of Differentiated Thyroid Cancers

Primary Tumor

To optimize outcomes a judicious decision needs to be made regarding the extent of surgery weighing benefits against potential morbidity. Morbidity of surgery is influenced by the volume and expertise of the surgeon [29]. Bilateral procedures for logical reasons place patients at a higher risk of complications than unilateral procedures [26]. Besides, differentiated thyroid cancers are indolent with an excellent prognosis in the majority of patients. This forms the premise of a debate to the optimum surgical procedure of hemi versus total thyroidectomy in DTC. Proponents of hemithyroidectomy suggest that it is associated with lower morbidity, recurrence in the contralateral lobe can be salvaged if needed and most importantly that there is no proven determent in survival with this approach. Advocates of total thyroidectomy argue that the procedure reduces the risk of recurrence and is not associated with a significantly higher rate of complications in experienced hands. Also, total thyroidectomy facilitates follow-up in that it increases the reliability of thyroglobulin as tumor marker postoperatively and helps in early disease detection should the recurrence occur.

Bilimoria et al. showed that the extent of surgery affects recurrence and survival in tumors >1 cm recommending total thyroidectomy in these patients from a large national cancer database (NCDB) of 52,173 patients [30]. Hay et al. studied the temporal trends in patients classified as low risk according to MACIS (distant metastasis, patient age, completeness of resection, local invasion and tumor size). About 70% of cases underwent lobectomy between 1940 and 1949, 22% between 1950 and 1959 and thereafter between 1960 and 1999, 91% of patients underwent total thyroidectomy. The results showed cause-specific mortality and tumor recurrence was significantly higher between 1940 and 1949 compared to between 1950 and 1999 [31]. Mazzaferri et al. in a study of 1355 patients reported that for tumors >1.5 cm near-total thyroidectomy followed by RAI ablation decreased tumor recurrence and mortality [32]. Meta-analysis of 2939 patients showed that for tumor size ≤1 cm thyroid lobectomy was associated with high recurrence rates [33]. Another meta-analysis analyzed the risk factors influencing recurrence in PTC and showed that tumor size >2 cm and subtotal thyroidectomy were significant in addition to other factors, including gender, ETE, lateral lymph node and distant metastases and receipt of radioactive iodine [34]. Recently published study of 5266 patients with tumors 1–4 cm showed that lobectomy is associated with higher recurrence rates and lower disease-free survival [35]. All these studies are in favor of total thyroidectomy in patients with tumor size >1–2 cm. There are studies however that are at variance with the above and favor hemithyroidectomy as an oncologically safe procedure for tumors up to 4 cm. Adam et al. in an updated analysis of NCDB of 61,775 patients showed that after adjustments for demographics, clinical factors and pathological factors; the overall survival (OS) of lobectomy and total thyroidectomy was similar for tumors between 1 and 4 cm [36]. Similarly, reports from the SEER database have shown that extent of surgery does not impact survival in these patients [37–39]. Nixon et al. similarly reporting on 889 patients with T1T2N0 tumors (<4 cm) showed that the extent of surgery does not impact OS, local or regional recurrence [40]. Recently published propensity scores matched-pair analysis comparing the outcomes of lobectomy versus total thyroidectomy in 2345 patients reported no DFS benefit with total thyroidectomy and suggested that the extent of surgery was not an independent factor predicting recurrence for tumor size between 1 and 4 cm [41].

This state of clinical equipoise between hemithyroidectomy and total thyroidectomy for tumors less than <4 cm prevails because of the lack of randomized-controlled trial (RCT) and conflicting results across many studies. To confound factors, making interpretation difficult all these studies are mainly retrospective in nature with heterogeneous patient populations and study outcomes.

To put the current literature in proper perspective there is no debate that in patients with a tumor less than 1 cm with no other high-risk feature (nodal metastasis, distant metastasis, prior history of radiation exposure or hereditary cancers) hemithyroidectomy is an adequate procedure while all tumors >4 cm should undergo total thyroidectomy. For tumors between size 1 and 4 cm either a total or hemithyroidectomy is considered adequate in the absence of other high-risk features. Total thyroidectomy is also preferred to facilitate postoperative radio-iodine treatment if deemed necessary by the treating clinicians based on tumor and patient characteristics and help follow-up. Patients and the family must be taken into confidence and counseled with regards to the pros and cons of either procedure and the decision taken in conjunction.

Unlike in other cancers, the prognostic detriment of lymph node metastasis in differentiated thyroid cancer is uncertain and usually does not impact outcomes in the majority. The first echelon of nodal spread in the majority of thyroid cancers is the central compartment, an area that extends from the hyoid superiorly to the innominate artery inferiorly and is bounded by the carotids on either side laterally. Given the risk to the RLN/parathyroids, routine prophylactic central compartment clearance is not recommended in early DTC with no high-risk features due to the possible morbidity associated with the procedure. Central compartment clearance is however recommended when there is nodal involvement, in locally advanced T3/T4 tumors and in the presence of lateral compartment metastasis (80% will have metastatic nodes in the central compartment) [20]. Lateral neck dissection is indicated only in the presence of metastasis and surgery should entail clearing level II–V. There is no role of "berry picking" given that this procedure is associated with a high rate of nodal recurrences.

3.3.2 Radioactive Iodine (RAI) Treatment

The indications and need for radioiodine have undergone a paradigm shift in the recent past with lesser patients being treated with RAI. ATA guidelines stratify thyroid cancers into low, intermediate and high risk (Table 2). High-risk cancers warrant RAI treatment while it should be considered for those with intermediate-risk. Schlumberger et al. conducted phase III 2 × 2 factorial RCT (ESTIMABL1) to compare the thyrotropin stimulation methods (thyroxine withdrawal versus recombinant human thyrotropin) and to determine the ideal dose of RAI (1.1 GBq versus 3.7 GBq) in low-risk thyroid cancers. The authors concluded that recombinant thyrotropin and low dose (1.1 GBq) were adequate for the management of low-risk cancers [42]. The long-term follow-up of the trial at the median follow-up of 5.4 years reconfirmed the findings and the results showed that the disease recurrence was not related to the ablation strategy [43]. Mallick et al. in a multicentric noninferiority trial (HiLo) similarly comparing the dose of RAI (30 mCi versus 100 mCi) and influence of using either recombinant human thyrotropin (thyrotropin alfa) or thyroid hormone withdrawal for T1–T3 DTC concluded that low dose and thyrotropin alfa were equally effective and were associated with lower rates of adverse events [44]. The long-term results of the trial confirmed the finding and reported a similar recurrence rate in the two arms [45]. Based on a recently published randomized controlled trial (ESTIMABL2), RAI is not routinely advocated for low-risk cancers [46]. The trial randomized 730 low-risk thyroid cancers and showed that follow-up without iodine ablation was non-inferior to iodine ablation strategy in terms of functional, structural, and biologic events at 3 years. There is another ongoing phase III trials comparing the outcomes of low dose RAI versus observation in low-risk thyroid cancers (IoN:NCT01398085) [47].

3.3.3 Radiation Management

The role of external beam radiotherapy in DTC is contentious and there is a paucity of published literature on this topic. The only multicentric prospective trial designed to establish the clinical benefit of external beam radiotherapy (EBRT) in locally invasive thyroid DTC was converted to a prospective cohort study due to patients' refusal to consent for randomization. EBRT showed a weak statistically not significant benefit in this trial and the authors recommended discontinuation of routine adjuvant EBRT in DTC [48]. The Endocrine Surgery Committee of the American Head and Neck Society suggest to consider EBRT in patients with gross residual or unresectable locoregional disease, and in older patients with a high probability microscopic residual disease which may not respond to RAI [49].

Jacomina et al. in a recent meta-analysis attempted to establish the indications of EBRT in DTC. The meta-analysis including 9 studies with 2981 patients compared oncologic

Table 2 Risk stratification of thyroid nodules (adapted from ATA guidelines): risk of disease recurrence

Risk category	Features	Recommendation for RAI	Recommended TSH levels (mU/L)
Low	Intrathyroidal PTC (2–4 cm) Minimally invasive FTC ≤5 Lymph nodes with micro metastasis (<0.2 cm)	Observe	0.5–2
Intermediate	Aggressive histology Lesion >4 cm in size with minimal ETE >5 Nodes (0.2–3 cm) Vascular invasion	Consider	0.1–0.5
High	Gross ETE, extensive vascular invasion in FTC, distant metastasis, lymph node >3 cm	Recommend	<0.1

PTC papillary thyroid cancer, *FTC* follicular thyroid cancer, *ETE* extrathyroidal extension outcomes and toxicity with and without RT. Results showed that the addition of adjuvant RT improves locoregional recurrence-free survival but it did not add any benefit to OS or distant metastasis-free survival. This advantage was observed in patients with advanced age, a locoregionally advanced disease with structural invasion and gross or microscopic residual disease [50]. Another systematic review of 16 studies including 5114 patients suggested benefit of EBRT in locoregional control in patients with advanced age >45 years at high-risk of locoregional recurrence [51]. However, there is a need for larger more robust data to establish the true role of adjuvant radiotherapy in DTC.

3.3.4 Thyroxine Replacement Post Thyroidectomy

The DTCs are TSH-dependent, and hence, patients should be administered supraphysiological doses of thyroxine as a replacement. A meta-analysis of 4174 patients showed that thyroid hormone suppression therapy after initial therapy decreased the risk of disease progression/recurrence and death [52]. However, high doses of thyroxine are known to be associated with diminished cardiac reserve, atrial fibrillation and premature osteoporosis [53, 54]. Therefore, the dose should be adjusted judiciously weighing the benefit against the morbidity. The suppression therapy does not offer any disease-free survival benefit in low-risk cancer patients [55]. The degree of suppression should be guided by the aggressiveness and risk of recurrence should be taken into consideration. The high-risk or recurrent tumor should undergo more aggressive thyrotropin suppression whereas it has to be less aggressive in low-risk tumors. Intermediate-risk tumors who are at high risk of adverse effects should undergo evaluation during the follow-up and dose titration [56]. Recommended TSH levels are 0.5–2.0 mU/L for low-risk, 0.1–0.5 mU/L for intermediate and <0.1 mU/L for high-risk patients [20]. The risk stratification of patients is dynamic and changes with time, e.g., a high-risk patient who stays disease-free for years is then treated as intermediate and subsequently low-risk. Similarly, a low-risk patient with recurrence is considered to be at intermediate/high-risk and thyroxine dose should be appropriately titrated.

3.4 Stage-Wise Prognosis with Current Treatment

Age is a strong prognosticator for DTC and has been considered in the AJCC cancer stage grouping. Age cut off of 45 years was considered as distinguishing between low and high-risk cancers. Recently Nixon et al. performed recursive partitioning analysis on 1807 patients and reported that age cut off of 56 and 54 years for patients without and with distant metastasis respectively years is an important predictor of disease-specific survival [57]. Following this study, the age cut off has been changed from 45 to 55 years in recent 8th edition American Joint Committee on Cancer (AJCC) staging. AJCC classifies disease <55 years as stage I in the absence of DM and stage II with DM irrespective of T and N stage. For the patients' age ≥55 years tumor size, extrathyroidal extension and distant metastasis are the independent prognostic factors. These factors are therefore taken into consideration for stage grouping. The 5- to 10-year OS for stage I and II cancers are between 97% and 100%; 88% and 95% for stage III and 50% and 75% for stage IV [16].

3.5 Management of Recurrent Disease Including Specific Palliative Measures

Management of advanced or metastatic cancer is a challenge due to the limited efficacy of radiotherapy and conventional chemotherapy. Hence, whenever possible surgery or RAI must be considered as the first choice. Chemotherapy is only considered in recurrent metastatic cancers that are radioiodine refractory or when surgical salvage is not possible. Conventional chemotherapy has a limited role in thyroid cancers. Fortunately, the genetic landscape of DTC demonstrates numerous genetic alterations rendering them suitable for targeted therapy. The common alterations are the BRAF point mutation, RET-PTC translocation and RAS point mutation. Also, vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) are associated with aggressiveness and metastasis and a potential target for treatment. Tyrosine kinase inhibitors (TKI) targeting these pathways have been widely researched and have demonstrated benefit. Both Sorafenib and Lenvatinib are molecules that have been researched in randomized trials in radioiodine refractory DTC. Sorafenib is an oral tyrosine kinase inhibitor targeting various VEFGRs 1–3, BRAF, RET/PTC and platelet-derived growth factor receptor (PDGFR) β. Lenvatinib is an oral multikinase inhibitor of VEGFRs 1–3, fibroblast growth factor receptors (FGFRs) 1–4, PDGFR α, RET and KIT signaling pathway. In Phase III randomized-controlled trial (DECISION) in radioiodine refractory locally advanced and metastatic DTC Sorafenib showed significant median progression-free survival (PFS) improvement over the placebo (10.8 months versus 5.8 months respectively). This benefit was seen across all prespecified clinical and biomarker subgroups irrespective of the mutation status [58]. Similarly, Lenvatinib, when compared to a placebo in phase III RCT (SELECT) in iodine refractory progressive thyroid cancer, demonstrated a significantly better median PFS (18.3 months versus 3.6 months, respectively) [59]. Interestingly this improvement in PFS was longer than that observed with sorafenib. Also, the median PFS in the placebo group was significantly lower than the expected 8 months indicating that patients enrolled in this trial may have had a more aggressive disease.

Targeted therapy should be used judiciously as they are often associated with significant toxicity impacting on the patients' quality of life (QOL). The mere presence of asymptomatic disease does not warrant the initiation of treatment. Documented progressive locoregional or distant metastatic disease and symptomatic patients are indications for systemic therapy. Stereotactic radiosurgery is an alternative for symptomatic progressive disease when suitable in metastatic DTC which does not respond to RAI therapy.

4 Medullary Thyroid Cancers (MTC)

4.1 Clinical Presentation

Medullary thyroid cancers constitute about 5% of thyroid cancers and could be hereditary (25%) or sporadic (75%). Hereditary MTC occurs in younger patients, are mostly bilateral, multicentric and could be part of the multiple endocrine neoplasia (MEN) syndrome. MTC commonly presents as a solitary nodule in sporadic cases. The palpable MTCs are associated with regional metastasis in >75% of cases causing involvement of both central and lateral compartments [60]. Skip metastasis is seen in about 20% of cases where the central compartment is negative and metastasis directly occurs to the lateral compartment [61]. MTC may be associated with pheochromocytoma (50%), parathyroid neoplasm (20%) and Hirschsprung's disease or cutaneous lichen amyloidosis (MEN 2A) [62]. In MEN 2B, the MTC is associated with pheochromocytoma in 50% of the cases along with oral mucosal, conjunctival, intestinal ganglioneuromas and marfanoid habitus [63, 64]. Occasionally these patients may present with symptoms of flushing and diarrhea which is secondary to a very high level of calcitonin. In such cases workup for distant metastasis should be done to rule out pulmonary or liver metastasis [65].

4.2 Evaluation and Work-Up

In addition to routine evaluation mentioned under section DTC, these tumors need work-up for the hereditary MTCs. Familial medullary carcinoma expresses germline mutation in rearranged during transfection (RET) proto-oncogene which is located on 10q11.2. It is inherited as an autosomal dominant trait with partial penetrance. Given that the index case may be the first manifestation of a familial origin in 5% to 9% of patients with MEN2A which can be as high as 50% in cases with MEN 2B, when these mutations arise de novo, a RET protooncogene test is ordered in all cases even in the absence of strong family history [64, 66]. The RET mutation can be present on many different exons of the chromosome 10q which results in different ages of manifestation of the disease as well as different biological aggressiveness and these mutations are therefore classified into highest-risk, high-risk and moderate-risk. RET mutation positive patients need to be appropriately counseled and screened for pheochromocytoma before surgery. First-degree relatives should also undergo testing. Given its high penetrance, there is a role of prophylactic thyroidectomy among relatives who carry the mutation and have not manifested yet with the disease. The age of performing this procedure is determined by the type of mutation and aggressiveness of the disease.

Given the high incidence of nodal involvement, distant metastasis and the possible association with pheochromocytoma as part of a MEN syndrome, cross-sectional imaging is mandatory for every case of MTC. This could either be a CECT of the neck, thorax and abdomen (which should be triple phase CECT to identify liver metastases) or PET-CECT. The PET-CECT is now gaining acceptance as a one-step investigation for these cancers [67].

Calcitonin can help diagnose MTC but is not routinely performed in the workup of thyroid cancer as it is not cost-effective given the low incidence of these cancers. It is, however, helpful to corroborate the diagnosis in cases where FNAC is unable to subtype the tumor. Serum calcitonin is however essential as it acts as a marker to diagnose recurrence and tumor progression. Tumors with calcitonin doubling time less than 6 months have a poorer prognosis compared to the ones with more than 2 years [68]. Carcinoembryonic antigen (CEA) is another marker that is used in follow up of MTC and is a sign of dedifferentiation of the tumor. These markers help in prognostication as well as help guide initiation of TKIs in the treatment of recurrent tumors. Baseline calcitonin of more than 500 pg/mL acts as a surrogate for distant metastasis and should be corroborated with appropriate imaging.

4.3 Treatment Philosophy and Surgical Management

In contrast to DTCs, the minimum surgery recommended for MTC is total thyroidectomy given the multicentric nature of the disease. Central compartment dissection is recommended in all cases except when surgery is a prophylactic thyroidectomy based on RET oncogene mutation. Serum calcitonin levels can also help direct the extent of neck dissection. Machens et al. in a study of 300 patients found that serum calcitonin level thresholds of 20, 50, 200 and 500 pg/mL were associated with ipsilateral central and lateral neck, contralateral central neck, contralateral lateral neck and upper mediastinum lymph nodes, respectively [69]. The extent of neck dissection is best decided factoring the clinical neck node status, imaging and serum calcitonin. Regional metastasis in lateral compartment warrants neck dissection clearing level II through V on the ipsilateral side while the decision to address the contralateral neck if node-negative on imaging should be guided based on the serum calcitonin level.

4.4 Radiation Management

There exists a lack of trials addressing the benefit of EBRT in MTC. Recently published systematic review of 4 cohort studies, 22 retrospective and 1 prospective study looked at the role of EBRT in MTC both in the adjuvant setting as well as a primary modality in unresectable cases. It demonstrated there was no OS benefit with EBRT. However, in patients with nodal involvement, ETE or residual disease, radiotherapy reduced the risk of locoregional recurrence [70]. The ATA guidelines for MTC recommend considering EBRT in patients who are at high-risk airway obstruction and locoregional recurrence including extensive nodal disease, ETE or residual disease [64]. It is also recommended in cases with locoregional recurrence in whom surgery would be associated with high morbidity and risk. MTC is nonfollicular in origin, the thyrotropin levels in these tumors should be maintained within normal limits after the initial surgery. MTC has a prognosis between DTC and anaplastic cancer. The 5- and 10-year overall survival in MTC ranges between 60–100% and 55–100% respectively in the absence of metastasis [71].

4.5 Management of Recurrent Disease Including Specific Palliative Measures

Targeted therapy has shown to be of benefit in MTC in a palliative setting. Vandetanib, an inhibitor of RET kinase, VEGFR and epidermal growth factor receptor (EGFR) signaling, was compared to placebo in inoperable locally advanced or metastatic MTC in 331 patients (ZETA trial). The PFS was significantly prolonged in the Vandetanib arm along with better objective response rate, disease control rate and biochemical response. OS could not be commented on in this trial as the data was immature for meaningful analysis [72].

Cabozantinib, TKI of hepatocyte growth factor receptor (MET), VEGFR 2 and RET, was compared with placebo in 330 patients with radiographic progression of metastatic MTC in a phase III RCT. The median PFS was significantly better with Cabozantinib compared to placebo (11.2 months versus 4 months). The 1-year PFS was 47.3% compared to 7.2% in the placebo-treated group. Higher PFS and response rate with Cabozantinib was observed across all subgroups irrespective of RET mutation status (familial or sporadic) [73]. The long-term outcome of the trial at a minimum follow-up of 42 months showed 5.5 months increase in median OS with Cabozantinib; however, the difference was not statistically significant (hazard ratio (HR), 0.85; 95% confidence interval (CI), 0.64–1.12; $p = 0.24$) [74].

5 Anaplastic Thyroid Cancers

Anaplastic cancers are most aggressive thyroid cancers which arise de novo or due to transformation in a DTC. These tumors portend a poor prognosis, grow rapidly and usually present in advanced stage precluding surgery in the majority of cases. However, whenever the disease is confined to the thyroid gland and deemed operable, surgery should be aimed for. The median survival of these cancers is 3–5 months and the 10-year survival rate <5% [75].

6 Parathyroid Cancers

Parathyroid carcinoma is rare and accounts for 0.005% of all cancers [76]. Presenting symptoms are nonspecific and often mimic primary hyperparathyroidism with raised calcium and parathyroid hormone (PTH) levels posing a diagnostic challenge. About 10% of the parathyroid carcinoma may be nonfunctional. The disease affects both males and females equally unlike benign hyperparathyroidism which is more common in females. Patients typically present in the fifth decade which is 10 years earlier than patients with primary hyperparathyroidism. These cancers are initially indolent but progressive causing local invasion. Surgery forms the mainstay of treatment with some role of adjuvant radiotherapy. Given its rarity, the prognostic factors are less clearly defined making formulation of guidelines difficult.

6.1 Incidence and Epidemiology

The entity was first described in 1904 by Swiss surgeon Fritz De Quervain [77]. The disease is mainly sporadic and etiology largely unknown. Studies have suggested a possible role of radiation exposure, end-stage renal disease and parathyroid adenoma or hyperplasia; however, a strong causal association with these conditions is lacking. The disease may present as a part of genetic syndrome commonly associated with hyperparathyroidism jaw-tumor syndrome (HPJT), an autosomal disorder characterized by ossifying fibromas of the mandible and maxilla in addition to parathyroid carcinoma. Other syndromic associations are with multiple endocrine neoplasia (MEN) 1, and familial isolated hyperparathyroidism [78].

6.2 Clinical Presentation

The clinical symptoms are mainly a result of hypercalcemia and frequently mimic benign hyperparathyroidism. However, the severity of symptoms is significantly higher in parathyroid carcinoma. The common symptoms are weakness, lethargy, fatigue, depression, impaired memory, weight loss along with abdominal symptoms like pain, peptic ulcers and pancreatitis. Patients may also present with renal and skeletal symptoms which are more commonly associated with carcinoma. Nonfunctioning parathyroid carcinomas (10%) tend to present with an atypical clinical picture often misleading diagnosis [79]. These patients present late and usually with neck masses due to the primary disease or regional metastasis. Patients may also present with metastasis in as high as 30% of patients. Neck mass, RLN palsy or signs of local invasion should prompt the diagnosis in favor of malignancy as these are fairly uncommon in conditions of benign hyperparathyroidism [80–82].

6.3 Evaluation and Work-Up

Parathyroid carcinoma is usually associated with serum calcium levels over 14 mg/mL. Parathormone acts as a reliable tumor marker both to establish the diagnosis and early detection of recurrence. PTH is markedly raised 10- to 15-fold higher than the normal [83]. Imaging (ultrasound, 4D computed tomography scan and technetium 99 sestamibi scan) helps in locating the site and extent of disease. Cross-sectional imaging is preferred to assess the extent when the local invasion is suspected. FNAC is not useful in establishing the diagnosis and may lead to seeding of the track. Parathyroid carcinoma is usually diagnosed on histopathology, which may, however, be difficult at times with equivocal pathological findings. Local invasion and metastasis (regional/distant) are the fundamental features of malignancy. Schantz and Castleman criteria that consider five histopathological features namely presence of a trabecular pattern, mitotic figures, thick fibrous bands, capsular invasion and blood vessel invasion is widely followed to help establish a diagnosis [82]. Features of invasion on histopathology are the sine qua non of the malignancy.

6.4 Principles of Management

Parathyroid carcinoma is best managed by a multidisciplinary team which should include an endocrinologist. Hypercalcemia which is often severe (>14–16 mg) and needs control in the preoperative and postoperative period. Surgery is the mainstay of treatment which should aim for complete removal of disease. Outcomes are dictated by the experience and expertise of the treating team [84, 85]. Patients are therefore best treated at tertiary centers having a dedicated team to manage these cancers.

6.4.1 Surgical Management

Parathyroid carcinoma is a surgical disease and resection should encompass en bloc excision of the tumor with negative gross and microscopic margins [86]. Some centers recommend more extensive surgery including thyroid lobectomy However, there is a lack of evidence that extensive surgery offers a survival benefit. Young et al. in a study of 136 patients showed that the extent of surgery (parathyroidectomy compared to en bloc resection and delayed thyroidectomy) did not improve survival [87]. However, inadequate surgery results in recurrence; rates as high as 49% were reported after the initial cancer surgery [88]. The incidence of lymph node metastasis is low, and hence, routine central compartment clearance may not be necessary for the clinico-radiological/at surgery node-negative disease [89]. Hsu et al. reported a study of 405 parathyroid carcinoma patients in which 114 patients had lymph node examination. Only 10.5% cases showed regional metastasis which was 7.5 times more frequent with tumor size ≥3 cm. Regional metastasis, however, was not an independent predictor of disease-specific survival [90]. Intraoperative PTH assay is a useful adjunct at surgery as the majority of tumors are secretory and drop in the levels guide the adequacy of surgery [80, 85].

6.4.2 Radiation Management

Parathyroid carcinomas are relatively radioresistant, and hence, the role of definitive radiotherapy (RT) is limited. Adjuvant RT, however, offers decreased local relapse rates and better locoregional control but the survival benefit is uncertain [84, 85, 91]. A case series from MD Anderson showed that although RT is well tolerated in these patients, whether it is beneficial and time of administration remains unclear [92]. Another recently published large series from NCDB of 885 patients showed that RT was not associated with survival benefit [93]. A large NCDB study of 1022 patients showed that relative risk of death was increased with old age, secondary malignancy, positive margin and lymph node positivity. The study however did not support the role of adjuvant RT for survival benefit [94]. The adjuvant radiotherapy should therefore be considered in presence of factors associated with high risk of locoregional recurrence like gross soft tissue invasion by disease, positive margins, nodal metastasis and recurrent cases.

6.4.3 Medical Management

There is no robust data to support the role of systemic therapy in parathyroid carcinoma. Literature is mainly contributed by anecdotal case reports and small series making interpretation difficult. The overall results have been unsatisfactory with chemotherapy and there is no standard regimen followed for the treatment of these tumors. Monotherapy using dacarbazine or combination of drugs fluorouracil, cyclophosphamide and dacarbazine or methotrexate, doxorubicin, cyclophosphamide and lomustine have shown some benefit in case reports [79, 81, 83].

6.5 Stage-Wise Prognosis with Current Treatment

AJCC 8th edition stages parathyroid carcinoma based on the extent of invasion of the primary tumor to the surrounding structures and not on the size, level of lymph node involvement and distant metastasis. The staging system however is premature as it is based on small retrospective studies with wide variation [95]. These are relatively indolent tumors with a reported 5- and 10-year OS of 86% and 49%, respectively [76].

6.6 Management of Recurrent Disease Including Specific Palliative Measures

Patients with surgically unresectable disease, recurrence and distant metastasis frequently develop hypercalcemic crisis. The medical challenge is to control the serum calcium level which otherwise can be fatal. Patients present with altered mental status and weakness as the result of hypercalcemia leading to excessive fluid loss secondary to vomiting and increased diuresis. Intravenous saline hydration with loop dietetics is the first essential step of treatment. Calcimimetic agents like cinacalcet, acting on a calcium-sensing receptor on the parathyroid gland and drugs blocking the osteoclast-mediated bone resorption like calcitonin and bisphosphonates help in decreasing serum calcium levels. There are studies to suggest the use of ethanol injections to ablate the unresectable disease and palliate symptoms but are not the routine standard of care [96].

7 How Do We Do It at TMC

7.1 Differentiated Thyroid Cancers

- Thyroid function test is the first investigation to be performed.
- Patients with clinical or subclinical hyperthyroidism undergo radionuclide scan and treated for the same.
- Other patients are evaluated further using USG. The reporting is done as per TIRADS and thyroid multimodal-imaging comprehensive risk stratification scoring (TMC RSS) [97].
- FNAC is performed for nodules >1 cm with high and intermediate, 1.5 cm with low and ≥2 cm with very low suspicion USG pattern.
- When extrathyroidal extension is suspected cross-sectional imaging is performed. CECT is also performed for node mapping as an adjunct to ultrasonography.
- Surgery is the mainstay of treatment which is hemithyroidectomy for nodules intraparenchymal ≤1 cm, total thyroidectomy >4 cm, hemi or total thyroidectomy between 1 and 4 cm based on high-risk factors or patients' preference.
- Therapeutic neck dissection in presence of regional metastasis.
- Role of prophylactic neck dissection in select cases.
- RAI ablation for high and intermediate risk DTC.
- Administration of supraphysiological doses of thyroxine for DTC. The TSH is to be maintained between 0.5–2, 0.1–0.5 and <0.1 mU/L in low, intermediate and high-risk patients.
- Follow-up frequency based on risk stratification with clinical examination, ultrasonography, serum Tg and RAI scan if indicated.

7.2 Medullary Thyroid Cancers

- Establishment of diagnosis: FNAC, serum calcitonin.
- Extent of disease: PET scan or CECT neck and thorax and triple phase CECT abdomen.
- Establishment of familial MTC: genetic testing to detect germline RET mutation; if positive then genetic counseling and screening for pheochromocytoma with plasma free metanephrines and normetanephrines.
- Minimum surgery in MTC is total thyroidectomy with central compartment clearance.
- Therapeutic neck dissection in patients with regional metastasis.

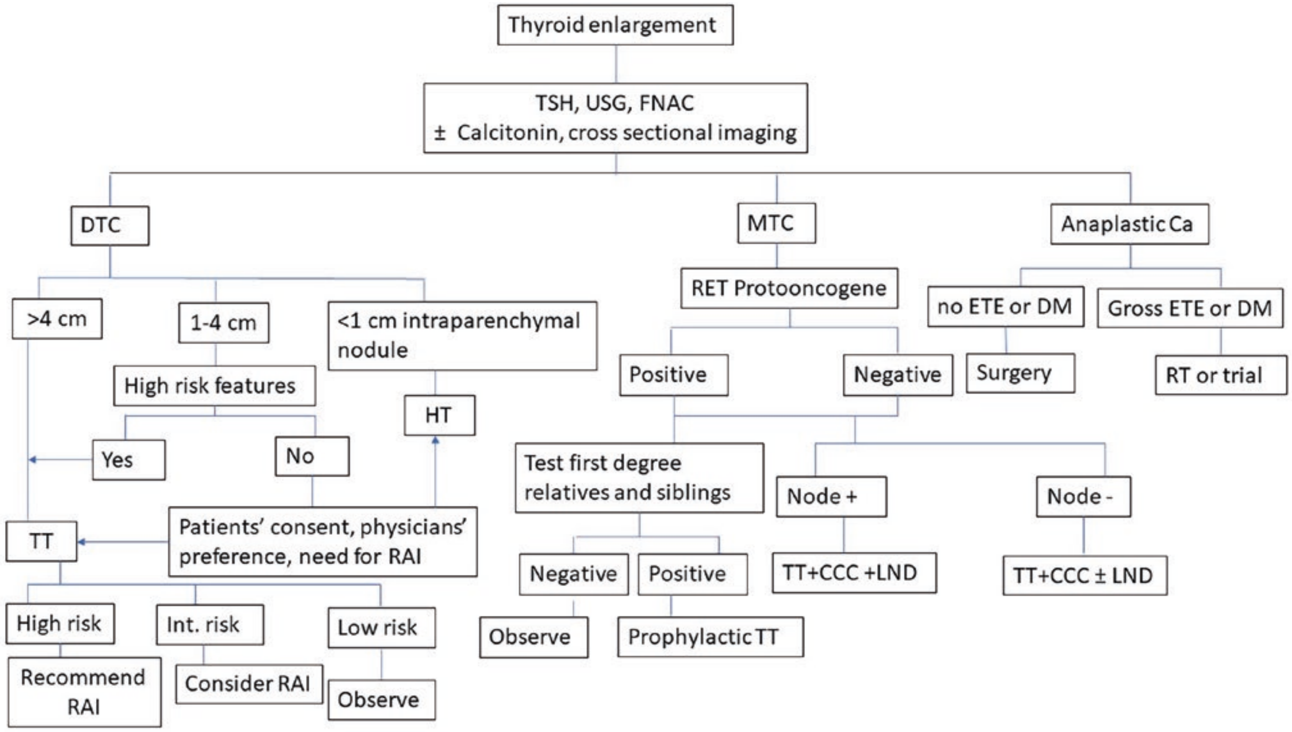
Thyroid enlargement
TSH, USG, FNAC
± Calcitonin, cross sectional imaging
DTC
MTC
Anaplastic Ca
>4 cm
1-4 cm
<1 cm intraparenchymal nodule
High risk features
Yes
No
HT
Patients' consent, physicians' preference, need for RAI
TT
High risk
Int. risk
Low risk
Recommend RAI
Consider RAI
Observe
RET Protooncogene
Positive
Negative
Test first degree relatives and siblings
Negative
Positive
Observe
Prophylactic TT
Node +
Node -
TT+CCC +LND
TT+CCC ± LND
no ETE or DM
Gross ETE or DM
Surgery
RT or trial

Fig. 1 Management of thyroid enlargement: work-up and treatment

- Prophylactic neck dissection based on the serum calcitonin level in node negative neck.
- Prophylactic total thyroidectomy for germline RET mutation positive siblings and first degree relative.
- Administration of thyroxine to maintain TSH within normal range.
- Follow-up with clinical examination, ultrasonography and serum calcitonin 3 monthly.
- Hereditary cases showed by followed up for pheochromocytoma and hyperparathyroidism.

7.3 Anaplastic Thyroid Cancers

- If operable, then surgery.

7.4 Parathyroid Carcinoma

- Raised serum calcium and PTH levels along with signs of hypercalcemia suggest the probability of PTH carcinoma.
- Surgery for parathyroid cancer is en bloc resection of parathyroid gland with negative gross and microscopic margins. Ipsilateral lobectomy and excision of adjoining structures if involved by disease, appropriate neck dissection.
- Serum PTH is a reliable tumor marker to detect recurrence in follow-up.

A management algorithm is presented in Fig. 1.

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Breast Cancer

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Abbreviations

ACT	Adjuvant chemotherapy
AI	Aromatase inhibitors
ALND	Axillary lymph node dissection
APBI	Accelerated partial breast irradiation
BCS	Breast-conserving surgery
Brm	Brain metastases
DFS	Disease-free survival
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ER	Estrogen receptor
FNR	False-negative rate
GnRH	Gonadotropin-releasing hormone
LABC	Locally advanced breast cancer
LAS	Low axillary sampling
NACT	Neoadjuvant chemotherapy
OPS	Oncoplastic surgery
PMRT	Postmastectomy radiotherapy
RCT	Randomized controlled trial
SFRT	Single-fraction radiation therapy
SLNB	Sentinel lymph node biopsy
SOFT	Suppression of Ovarian Function Trial
SRS	Stereotactic radiosurgery
TEXT	Tamoxifen and Exemestane Trial

1 Introduction

Breast cancer is the commonest cancer in Indian women [1] with the age-adjusted incidence rate and mortality per 100,000 women of 25.8 and 12.7, respectively [2]. The incidence is different in urban and rural India, with one-third in urban areas and one-ninth in rural areas [3]. Overall, the stage distribution ranges from 40% to 50% for early, 30% to 40% for locally advanced and 5% to 10% for metastatic setting [1]. Early dissemination of the breast cancer cells provides rationale for adjuvant systemic therapy which substantially reduces the risk of distant recurrence and breast cancer mortality.

2 Predictive and Prognostic Markers

Prognostic factors are surrogate markers of the aggressiveness that provide information on the inherent biological behavior of the disease in the absence of any type of adjuvant systemic treatment.

The most significant clinicopathologic prognostic factors [4] include stage (determined by the tumor size and extent of axillary lymph node involvement) [5] and histologic grade (assessed by the Nottingham method or the Elston–Ellis modification of the Scarff–Bloom–Richardson system) [6]. Young age at presentation, menopausal status, presence of lymphovascular emboli and extracapsular nodal extension form independent adverse prognostic factors [7–10]. Ki67 expression, a marker of tumor proliferation, impacts disease-free survival [11]. Mitotic index has been found to be a

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strong predictor of survival in node-negative breast cancer patients [12].

Predictive factors are indicative of response of the tumor to specific therapies and therefore can help guide treatment management. Steroid hormone receptors were originally classified as markers with prognostic significance but lost this advantage with prolonged follow-up [13]. Steroid hormone receptors (ER/PR) are predictive markers in the adjuvant setting and HER2/neu receptor is both a strong predictive and prognostic marker. HER2 status is predictive of response to anti-HER2-targeted therapies like Trastuzumab and Pertuzumab [14]. Recent evidence also suggests increased sensitivity of HER2+ tumors to anthracycline-based chemotherapy [14].

Ki67 (marker of proliferation) is a nuclear antigen, which is both a prognostic and predictive factor in early breast cancer, and is used to decide response to chemotherapy [15]. A higher nuclear grade and overexpression of p53 [16] has a direct correlation with higher Ki67. A number of studies [17, 18] have reported that a higher Ki67 index correlates with larger T size, positive lymph nodes and lymphovascular invasion. The variability of correlation may be attributed to the cut off values for Ki67, as Ki67 has been divided based on ≥10% and <10% in some studies and in other studies based on ≥20% and <20%.

Gene signature panels are available like the *Oncotype DX* (21-gene assay) [19], *Mammaprint* (70-gene profile) [20, 21], *Breast Cancer Index* (two gene recurrence score and a five gene tumor molecular grade index) [22, 23] and *Prosigna* (50-gene classifier) [24]. They provide prognostic information over and above standard factors and direct evaluation of the risk–benefit ratio of adjuvant systemic therapy for node-negative breast cancer. The OncotypeDX RS assay is useful as a decision-making tool in node-negative hormone receptor-positive breast cancer patients [25] and even in some 1–3 LN-positive cases [26].

Online tools are available to prognosticate the disease and aid clinical decision making with respect to adjuvant therapy. *Adjuvant! Online* provides estimates of the risk of disease recurrence or death at 10 years [27]. *Predict* calculates the relative reduction in mortality with multiple lines of chemotherapy and hormone therapy [28]. Validation of these online tools in specific geographic locations is needed before routine use, due to possible differing biological characteristics compared to the original validation cohorts.

3 Principles of Management

3.1 Early and Locally Advanced Breast Cancer

Surgery is the mainstay of treatment. Over the years, the original Halstedian theory has given way to Fisher's theory that breast cancer is a systemic disease at inception. This has led to a paradigm shift toward conservation in locoregional treatment with the advances in systemic therapy. The principle of loco regional therapy is based on eradication of all malignant cells from the breast and the draining nodal basin. Adjuvant therapy includes systemic chemotherapy followed by radiation and hormonal therapy. The goal of systemic therapy is eradication of the microscopic disease present in the body in the form of occult metastasis. There are various lines of chemotherapy which can be used in combination with targeted therapy. Radiation helps to achieve loco regional disease control.

3.2 Metastatic Breast Cancer

The goal of treatment is disease control and palliation of symptoms. For hormone receptor positive with low disease burden, endocrine therapy can be started as the first-line treatment. There is good response observed in approximately 30% to 40% patients with disease stabilization in another 20% [12]. If the disease burden is high, systemic therapy is indicated with maintenance hormone therapy. If HER2/neu is overexpressed/amplified, anti-HER2-targeted therapy agents are also indicated. Bisphosphonates are added for bone metastasis. Surgery is reserved for bleeding or fungating tumors [29]. Radiation is used for metastatic sites in the bone or brain or occasionally a bleeding tumor in an unfit patient.

4 Imaging

4.1 Screening

The role of mammography as a screening tool has been criticized over the years. Sensitivity of mammography in a premenopausal population is low and efficacy as a screening tool has been debatable. In women above 50 years of age, mammography has shown a reduction in mortality, but at the cost of increase in the over-diagnosis of approximately 25% after 25 years of follow-up [30]. In contrast, CBE results in minimal over-diagnosis as shown in the randomized studies on CBE versus not. In the studies evaluating CBE as a single modality, all cancers detected were invasive or palpable preinvasive tumors.

4.1.1 Current Status of Screening for Breast Cancer

The US Preventive Services Task Force recommendations for screening suggest performing a mammogram every 2 years in women aged 50–74 [31]. The updated results of the age trial have however indicated some additional benefit of screening for women aged 40–50. The updated results of the AGE trial suggested reducing the lower age limit for screening from 50 to 40 years could potentially reduce breast cancer mortality, though most cancers were identified in women after 50 even in that trial [32]. Additionally, clinical breast examination conducted biennial, results in down staging and reduces mortality by 30% in women over the age of 50 years [33].

Screening recommendations for breast cancer are listed in Table 1.

Table 1 Screening recommendations for breast cancer

- Awareness and breast self-examination as a tool for awareness in woman of all ages.
- Not enough evidence to support screening mammogram in women <50 years of age.
- For premenopausal women, awareness of breast cancer.
- Annual clinical breast examination and awareness about breast cancer of biennial mammography in healthy women over the age of 50 years.
- However, the 25% probability of overdiagnosis must be kept in mind when recommending mammography as a screening tool.
- High-risk individuals (BRCA-positive, significant family history) to be treated as per standard guidelines.

Abnormalities detected on screening mammograms will often be nonpalpable lesions like microcalcifications, masses or focal areas of architectural disturbance (Fig. 1). Some of these lesions may be seen on correlative ultrasound, which helps in targeting the biopsy. USG-guided biopsy is a real time biopsy that is more comfortable for the patient and is preferred if the lesion is identified on USG (Fig. 2). For the abnormalities that are seen only on mammograms, vacuum assisted biopsy (VAB) devices are able to obtain almost complete excision of small lesions under stereotactic guidance. Another method is hook wire localization, either with stereotaxy or manually, followed by complete excision of the area of abnormality (Fig. 3). VAB is expensive; however, it is fully done under guidance while the hook-wire excisions require coordination between the mammography and surgical teams.

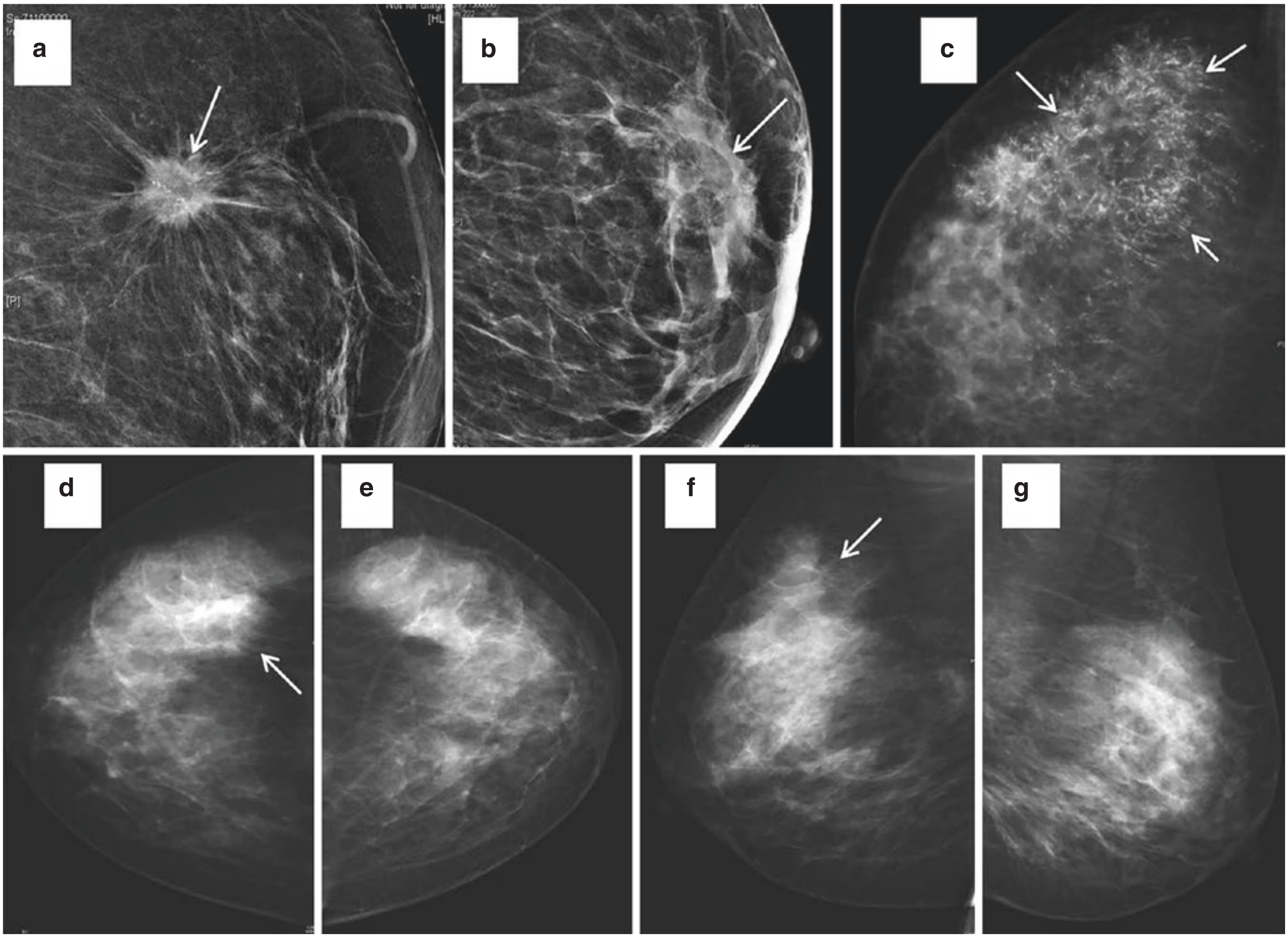


Fig. 1 Types of manifestations of breast cancer on mammograms. (**a**) A classical spiculated mass with microcalcifications (arrow). (**b**) An area of architectural distortion (arrow). (**c**) Regional pleomorphic microcalcifications (outer limits marked by arrows). (**d**) Right CC, (**e**) left CC, (**f**) right MLO and (**g**) left MLO views of the same patient showing asymmetric increased density in the right upper outer quadrant marked by arrows. This was caused by a mass

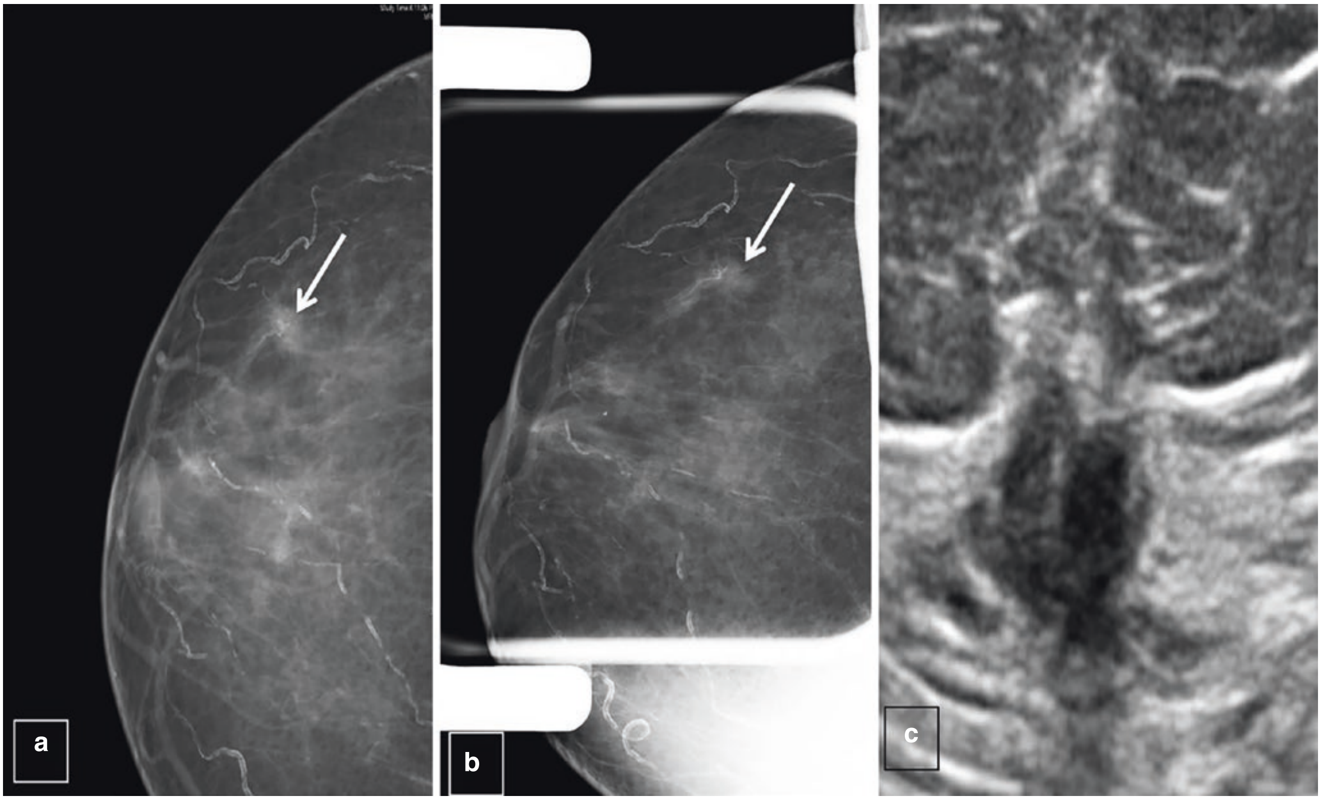


Fig. 2 In the screening craniocaudal view of the mammograms (**a**) a small irregular density is seen which is first confirmed by a spot compression view (**b**) and also seen as a hypoechoic solid mass with irregular shape and irregular margins on the ultrasonography images (**c**). The lesion can then be sampled for histopathology under ultrasound guidance

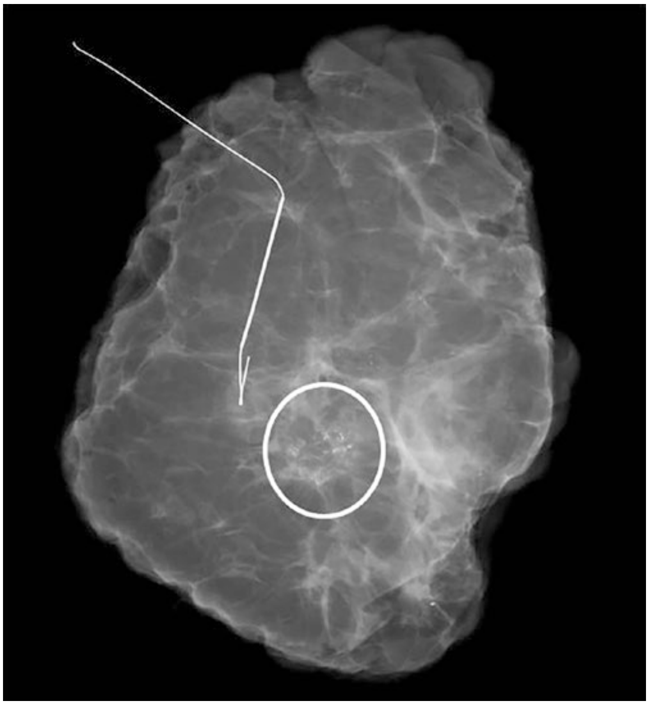


Fig. 3 Specimen radiograph showing pleomorphic microcalcifications (encircled) with a hook wire adjacent to them

4.2 Diagnostic Imaging

The current role of mammography is diagnostic, to evaluate the ipsilateral breast for number of lesions and to help map the extent of disease (if the woman is keen on breast-conserving surgery) and to screen the opposite breast at the time of surgery (less than 4% women may have a contralateral lesion). The sensitivity of mammogram depends on the breast density on mammogram (Fig. 4).

A combination of MG and USG can detect additional lesions than either of them alone but USG has a high false-positive rate [34]; hence, it is not routinely recommended in all patients. It can be used in cases when there the breasts are dense and the mass is occult or when there is clinical suspicion of multiple tumors. USG also serves as an adjunct for characterization of the mass, especially to differentiate a cystic one lesion from solid. MRI is not recommended as a preoperative test for evaluation of ipsilateral breast in all patients diagnosed with breast cancer, even when a breast conservation surgery is planned. The COMICE trial a randomized controlled trial (RCT) that showed that no benefit with the addition of MRI to triple assessment in patients undergoing BCT [35]. The MONET trial demonstrated adverse effect of

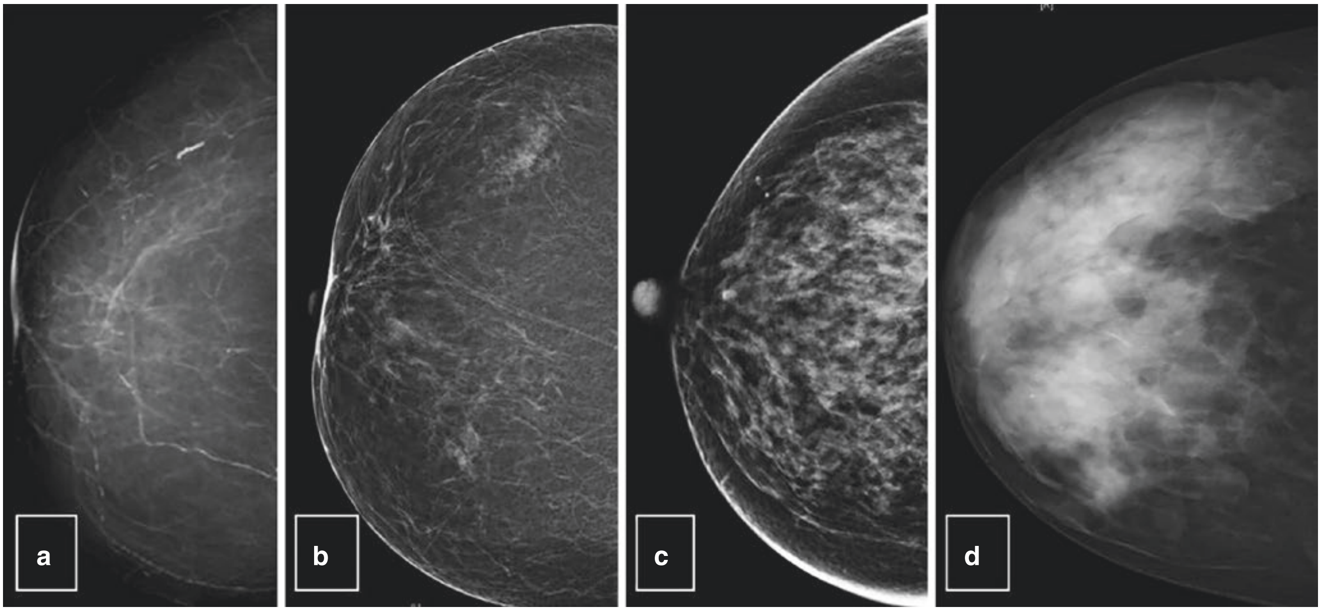


Fig. 4 This composite image illustrates the different types of normal breast parenchyma, with images from left to right showing increase in proportion of fibro-glandular tissue which leads increasing breast density. The sensitivity of mammography decreases with increasing breast density. (**a**) fatty breast, (**b**) scattered fibroglandular density, (**c**) heterogeneously dense, (**d**) extremely dense

MRI in the form of increased re-excision rates in patients undergoing MRI [36].

Housammi et al. in an individual patient data meta-analysis evaluating the association between preoperative breast MRI and local and distant recurrence in patients with breast cancer suggested that preoperative MRI is not associated with reduced risk of local or distant recurrence, at 8-year recurrence-free survival [37]. However, MRI breast may be considered when the diagnosis of lobular carcinoma is made as there is an increased incidence of multifocal/bilateral tumors. MRI is also useful in cases such as those with Paget's disease with dense breast on mammograms and no identifiable primary, metastatic axillary adenopathy and negative dense mammograms (EUSOBI guidelines).

5 Surgical Management

5.1 Management of Primary

Surgical management has evolved from the era of Halstedian radical mastectomy to lumpectomy and breast conservation. There has been a paradigm shift toward conservation, both of the primary and the axilla.

Landmark studies like NSABP B-06 compared mastectomy to lumpectomy with or without radiation. Cumulative incidence of IBTR was 39.2% for the lumpectomy alone arm and 14.3% for the lumpectomy with RT arm ($P < 0.001$) [38]. We have now shifted to an era of oncoplastic breast surgery.

Oncoplastic surgery (OPS) allows for wide excision without compromising principles of oncology and integrates plastic surgery techniques for immediate breast reshaping. Oncoplastic techniques range from simple reshaping and mobilization of breast tissue to more advanced mammoplasty techniques. With improving survival, cosmetic outcome and quality of life have come to the forefront and the future of surgery for breast cancer lies in integrating principles of OPS into our practice.

The selection of the oncoplastic surgical technique is based on numerous factors, for example patient's breast size, lesion location and volume of breast tissue excised (Table 2).

Local recurrence: In conventional breast-conserving surgery (BCS) local recurrence rates are reported between 10% and 14%, while in oncoplastic surgery, rates are documented at 2% and 9%. The possible explanation is that OPS usually entails wider excision. Rainsbury [39] reported local recurrence for volume displacement to be 0% to 7%, and of volume replacement to 0% to 5%. Clough et al. [40] reported local recurrence rate of 9.4% with OPS (Table 3).

Breast reconstruction: The decision about breast reconstruction (BR) is often multifaceted, including patient perceptions and surgeon expertise and available donor sites. In a large survey conducted among patients treated for breast cancer who had undergone a mastectomy, 20% said they would consider secondary reconstruction. The remaining patients possibly have high coping skills or are satisfied with the external prosthesis [41].

Post chemotherapy BCS: Breast conservation for locally advanced tumors is an option in well selected cases as is

Table 2 Classification of oncoplasty

Based on timing

Depending upon when the plastic surgical procedure is carried out, there are three options:

1. Immediate—At the time of primary surgery
2. Delayed immediate—1–2 weeks following primary surgery (usually after histopathological confirmation)
3. Delayed—Anytime following radiation

Based on technique

Oncoplastic procedures, for convenience, are divided as

1. Volume displacement procedures
2. Volume replacement procedures

Table 3 Risk factors for local recurrence following BCT

These factors can be divided into patient-, tumor- and treatment-related factors

Patient-related factors:

1. Age
2. Inherited susceptibility: presence of hereditary breast and ovarian cancer syndromes

Tumor-related risk factors:

1. Positive resection margins
2. Molecular subtypes
3. Treatment-based risk factors
4. Use of boost to the tumor bed
5. Adjuvant systemic therapy

shown by the various prospective and retrospective cohort studies [42]. The recent EBCTCG review on BCS post NACT highlights the importance of accurate localization techniques pre NACT to mark the tumor bed appropriately [43].

5.2 Approach to Axilla

Management of axilla has evolved from complete axillary dissection to sentinel node biopsy. Axillary lymph node dissection (ALND) remains the standard for patients with node-positive disease (with histologic confirmation). A complete axillary dissection is still carried out in most node-positive cases. A clinicoradiologically node-negative axilla has a 30% to 40% possibility of harboring occult metastatic disease [44]. National Comprehensive Cancer Network guidelines recommend to clear level I and II of the axilla [45]. However, in cases with 4 or more positive axillary LN, the probability of positive level III LN was as high as 53.2% [46]. Almost 50% of patients with high level I and II nodal burden run the risk of having residual disease in the axilla after surgery if level III is not addressed.

Axillary conservation: NSABP B-32 was a randomized trial that demonstrated the safety of avoiding ALND when the sentinel node is negative. Following this landmark study, sentinel lymph node biopsy (SLNB) is the standard procedure in clinically node-negative cases [47]. A validation study carried out for "low axillary sampling" (LAS) by Parmar et al. at TMH in 478 women with clinically N0 axilla yielded a false-negative rate (FNR) of 10.5% for LAS compared to 12.7% for SLNB [48]. In a resource constrained setting, LAS can be used as an acceptable alternative to SNB (Fig. 5).

1–2 LN positive: Women with SLN-positive breast cancer can either be considered for complete axillary dissection, or in cases of 1–2 LN positive can be considered for no further treatment to axilla or axillary radiotherapy [49, 50].

The results from the ACOSOG Z0011 [49] trial concluded that women with T1–T2, breast cancer, who had 1 or 2 positive SLNs, and were treated adjuvant systemic therapy and whole breast irradiation could be spared an ALND. However the study enrolled a large proportion of on pT1, low grade, micometastatic LN-positive patients. A similar audit reported from an Indian cohort, reported less than 10% of patients treated a tertiary cancer center [51] were similar low-risk disease and the authors recommend caution in extrapolating the results of the ACOZOG Z0011 trial to the general population of 1–2 SLN-positive EBC.

Multiple studies [52, 53] have evaluated risk factors for NSLN metastasis, including T size, grade, number of positive SLN, macrometastases and lymphovascular invasion and extranodal involvement.

Postchemotherapy axillary conservation: The role of conservative axillary surgery is not as robust in the post-chemotherapy situation. Numerous trials [54–57] have evaluated the role of SLN/LAS in the post NACT setting and current recommendations include the use of targeted axillary dissection, more than 3 SLN identified and dual dye technique [58].

Stage-wise management algorithms are presented in Figs. 6, 7, 8 and 9 [59].

Fig. 5 Low axillary sampling (**a**) perioperative and (**b**) anatomical illustration of axillary sampling) [43]

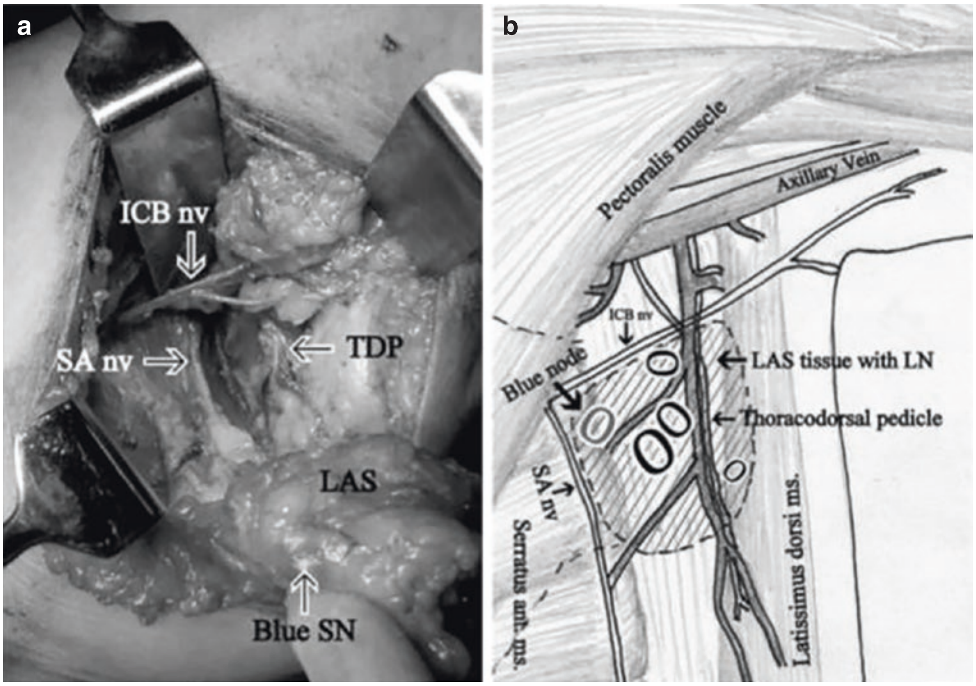

a
ICB nv
SA nv
TDP
LAS
Blue SN
b
Pectoralis muscle
Axillary Vein
ICB nv
Blue node
LAS tissue with LN
Thoracodorsal pedicle
SA nv
Serratus ant. ms.
Latissimus dorsi ms.

Fig. 6 Approach to axilla

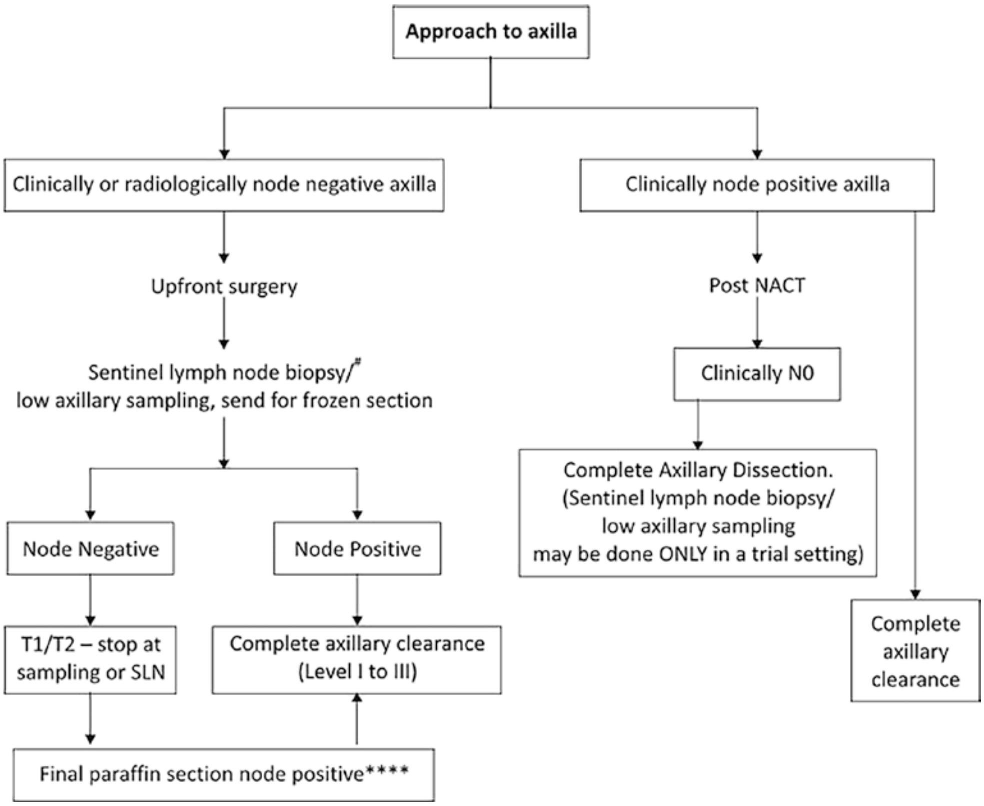

Approach to axilla
Clinically or radiologically node negative axilla
Clinically node positive axilla
Upfront surgery
Post NACT
Sentinel lymph node biopsy/#
low axillary sampling, send for frozen section
Clinically N0
Complete Axillary Dissection.
(Sentinel lymph node biopsy/
low axillary sampling
may be done ONLY in a trial setting)
Node Negative
Node Positive
T1/T2 – stop at sampling or SLN
Complete axillary clearance (Level I to III)
Complete axillary clearance
Final paraffin section node positive****

Fig. 7 Stage-wise management algorithm for operable/early breast cancer (OBC)—T1–2, N0–1, M0

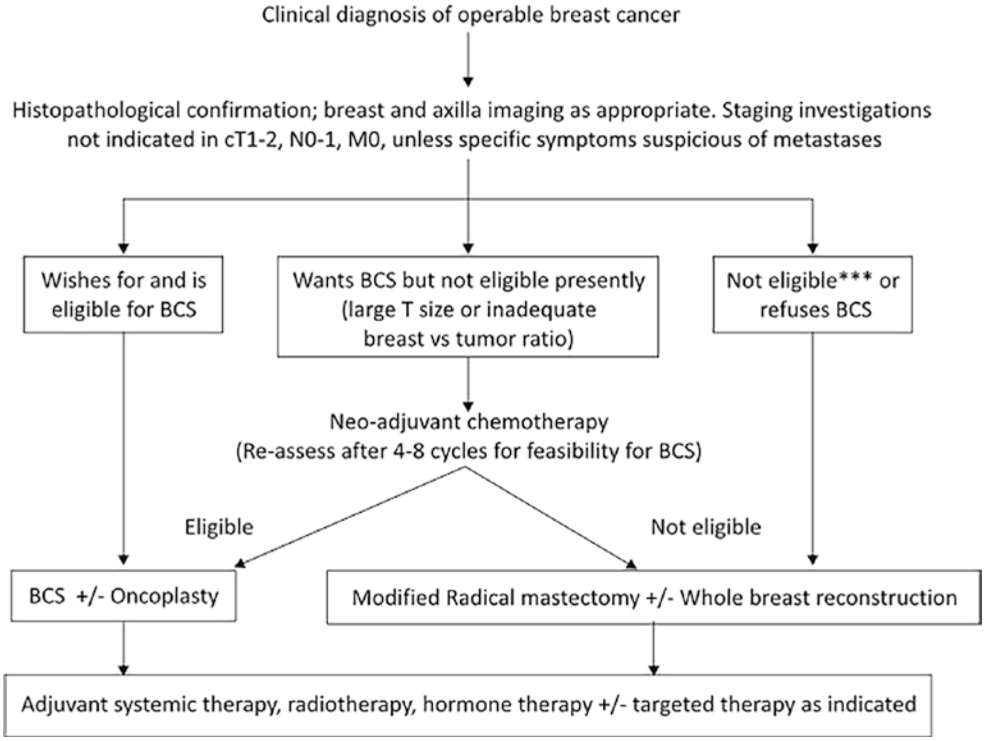
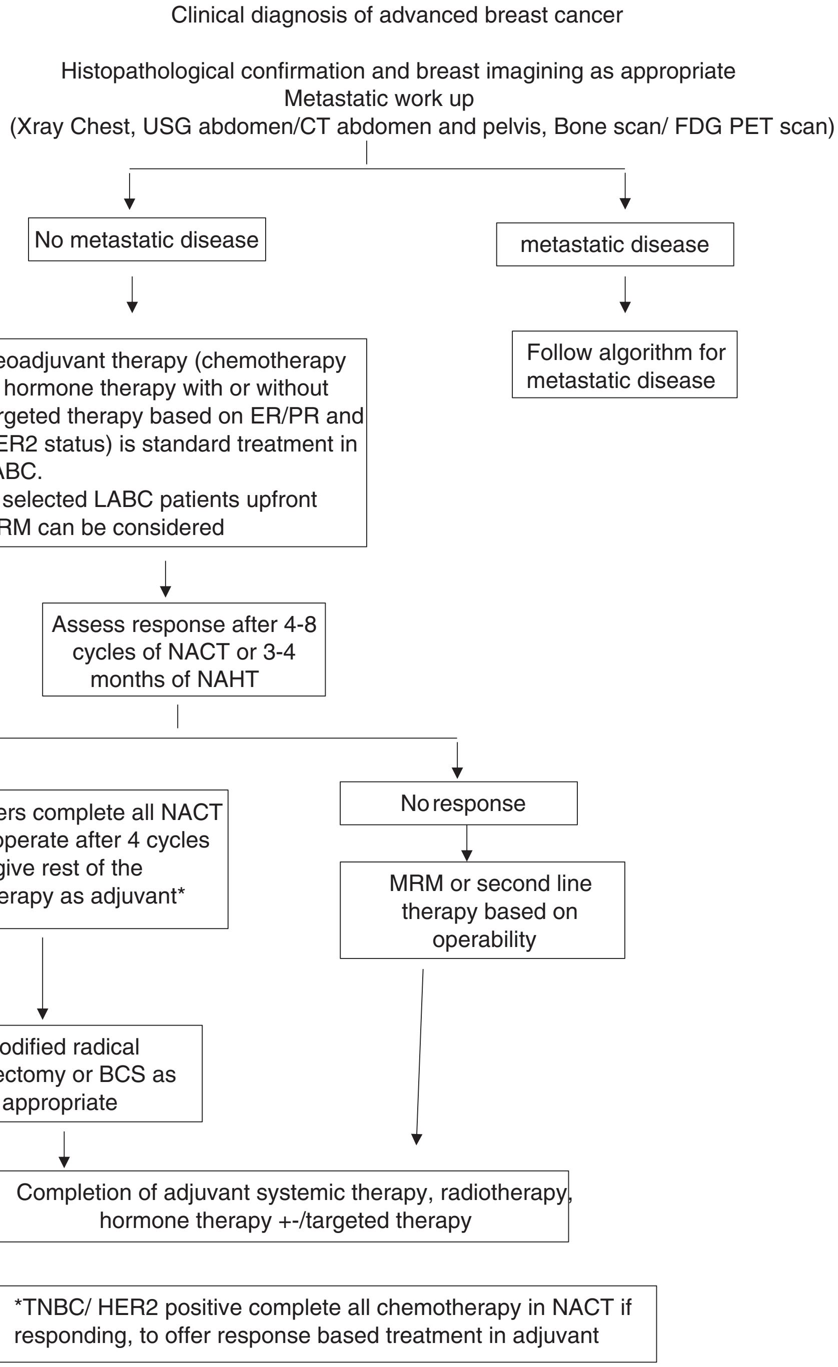

Clinical diagnosis of operable breast cancer
Histopathological confirmation; breast and axilla imaging as appropriate. Staging investigations not indicated in cT1-2, N0-1, M0, unless specific symptoms suspicious of metastases
Wishes for and is eligible for BCS
Wants BCS but not eligible presently (large T size or inadequate breast vs tumor ratio)
Not eligible*** or refuses BCS
Neo-adjuvant chemotherapy (Re-assess after 4-8 cycles for feasibility for BCS)
Eligible
Not eligible
BCS +/- Oncoplasty
Modified Radical mastectomy +/- Whole breast reconstruction
Adjuvant systemic therapy, radiotherapy, hormone therapy +/- targeted therapy as indicated

Fig. 8 Stage-wise management algorithm for locally advanced (LABC)—T3–4 any N, N2–3 any T, M0


Clinical diagnosis of advanced breast cancer
Histopathological confirmation and breast imagining as appropriate
Metastatic work up
(Xray Chest, USG abdomen/CT abdomen and pelvis, Bone scan/ FDG PET scan)
No metastatic disease
metastatic disease
Follow algorithm for metastatic disease
Neoadjuvant therapy (chemotherapy or hormone therapy with or without targeted therapy based on ER/PR and HER2 status) is standard treatment in LABC.
In selected LABC patients upfront MRM can be considered
Assess response after 4-8 cycles of NACT or 3-4 months of NAHT
In responders complete all NACT upfront or operate after 4 cycles and give rest of the chemotherapy as adjuvant*
No response
MRM or second line therapy based on operability
Modified radical mastectomy or BCS as appropriate
Completion of adjuvant systemic therapy, radiotherapy, hormone therapy +-/targeted therapy
*TNBC/ HER2 positive complete all chemotherapy in NACT if responding, to offer response based treatment in adjuvant

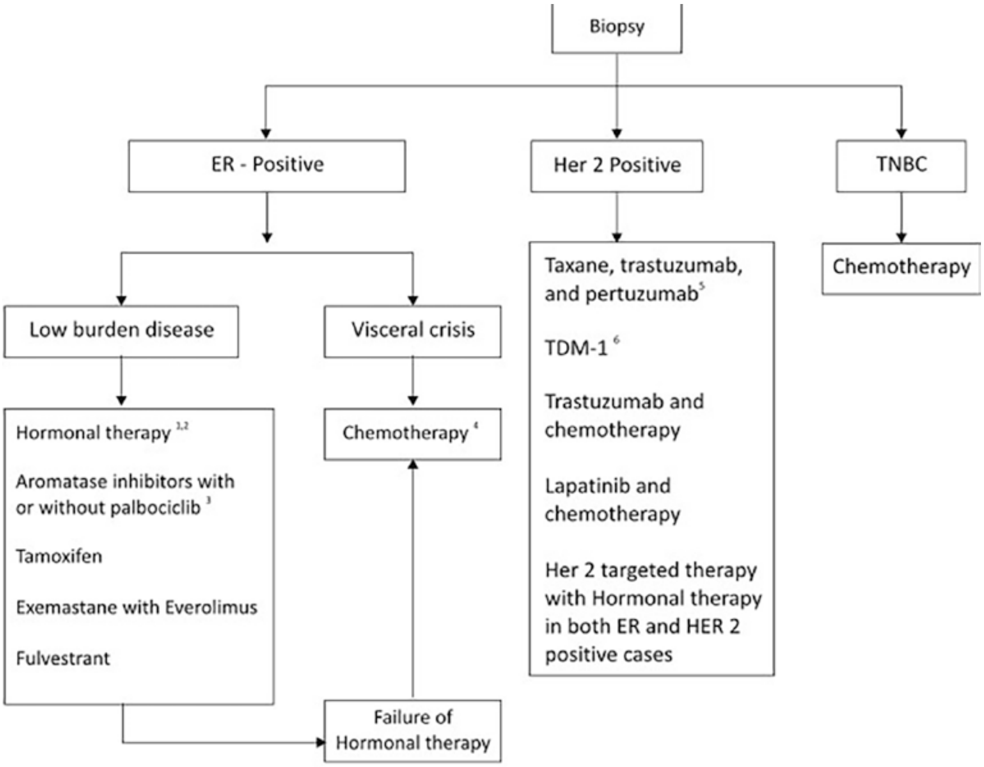

Biopsy
ER - Positive
Her 2 Positive
TNBC
Low burden disease
Visceral crisis
Hormonal therapy 1,2
Aromatase inhibitors with or without palbociclib 3
Tamoxifen
Exemastane with Everolimus
Fulvestrant
Chemotherapy 4
Failure of Hormonal therapy
Taxane, trastuzumab, and pertuzumab 5
TDM-1 6
Trastuzumab and chemotherapy
Lapatinib and chemotherapy
Her 2 targeted therapy with Hormonal therapy in both ER and HER 2 positive cases
Chemotherapy

Fig. 9 Stage-wise management algorithm for metastatic breast cancer (MBC)

6 Role of Radiotherapy

6.1 BCS

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis for breast conservation has shown that adjuvant RT reduces the absolute 10-year risk of local recurrence by 15.4% and 21.2% and 15-year risk of breast cancer mortality by 3.3% and 8.5%, respectively, in node-negative and node-positive women [60]. Following BCS, adjuvant RT to the whole breast with or without boost to the tumor bed is warranted in all patients.

It is prudent to deliver additional dose to the tumor bed as the long-term results of the large EORTC 22881-10882 trial have shown that a sequential 16 Gy boost to the tumor bed following 50 Gy to the whole breast confers improved local control across all age groups with maximum absolute benefit observed in women younger than 40 years (20-year risk 36.0% vs. 24.4%) [61]. However, boost also results in significant increase in the rates of severe fibrosis with a 10-year rate of 4.4% versus 1.6% when boost is not given ($P < 0.0001$).

6.2 Postmastectomy

For patients undergoing upfront MRM for early breast cancer, adjuvant RT is advised for patients with ≥4 positive lymph nodes irrespective of tumor stage. The recently conducted meta-analysis by EBCTCG showed that postmastectomy radiotherapy (PMRT) results in significant reduction of locoregional relapse (RR 0.68 for 1–3 nodes and RR of 0.79 in >3 positive LNs) as well as mortality (RR 0.80 for 1–3 LN and RR 0.87 for >3 positive LNs) [62].

6.3 Regional Lymph Node Irradiation

6.3.1 Axilla

The management of axilla has seen a major paradigm shift with a trend toward an axillary sparing approach to minimize morbidity in both patients with negative axilla as well as in case of limited positivity. The AMAROS and ACOZOG Z-11 study support the use of axillary radiation therapy in patients with SNB positive who have not undergone ALND [49, 50]. However, these studies include most patients with low-risk cancers with micrometastatic lymph nodes.

6.3.2 Other Regional Sites

Recently published studies like the MA 20 [63] and the EORTC 22922 [64] support comprehensive regional nodal irradiation but do not clarify as to which nodal region contributed toward maximum benefit. The benefit of treating nodal regions in a clinically T3N0 patients is not reported directly and current institutional practice is to treat supraclavicular region with RT for all locally advanced breast cancers. Internal mammary nodal chain is included if it is radiologically proven to harbor metastases prior to initiating any cancer directed treatment. Inclusion of extensive lymph nodal regions increases the risk of normal tissue toxicity and compels usage of complex techniques to achieve acceptable dose distribution.

6.4 Dose Fractionation

Hypo-fractionation implies delivery of fewer and larger doses of radiation (with a lower total dose). Mature results of the large phase 3 randomized trials from England and Canada and their meta-analysis not only confirmed the equivalence of hypofractionated regimen to the conventional regimen (comprising of total dose of 45–50 Gy in 25 fractions over 5 weeks with daily dose of 1.8–2.0 Gy per fraction) for local control but also reported that breast shrinkage, telangiectasia and breast edema were significantly less frequent with the hypo-fractionated regimen [65]. The ASTRO has also recently updated their guidelines on the use of hypofractionation for whole breast RT [66].

Recent Publication from the UK-FAST (28.5 Gy arm) and the FAST-Forward (26 Gy arm) studies show that 5 fraction RT either delivered once a week or daily is equivalent to the 5 or 3 weeks conventionally fractionated and moderately hypofractionated regimen [67, 68] respectively. The UK-FAST study included low-risk, hormone receptor-positive, node-negative patients older than 50 years who did not merit tumor bed boost. However, the UK-FAST Forward study was a pragmatic trial that included all patients T1–T3 and N0–1. The recent publication has only reported the safety and 5-year clinical outcomes for node-negative patients. As per the acute toxicity data on daily 5-fraction regimen, patients undergoing daily 5-fraction RT tend to develop acute toxicities 2 weeks after treatment completion. However, the grade of all the toxicities are similar except higher induration outside the tumor bed [1.90 (1.15–3.14), $P = 0.013$]. The 5-fr regimen can be adopted safely for low-risk node-negative patients at centers with appropriate quality assurance program as required by the study. This will help to improve access and ease of receiving RT and subsequently improve the breast conservation rates especially among lower and middle-income countries.

6.5 Accelerated Partial Breast Irradiation (APBI)

In optimally selected women, this can be accomplished by various means like brachytherapy (interstitial or balloon), external beam techniques (electrons, 3DCRT, IMRT, IGRT, protons) or intraoperative RT [69]. Due to the diversity of inclusion criteria, sample size, techniques and dose fractionation regimes used in various randomized studies, the efficacy and toxicity results vary considerably. Interstitial brachytherapy is the safest technique as this has been proven to be noninferior and less toxic to conventional whole breast RT in a large European phase 3 trial and is supported by long-term outcome from various institutional series [70–72].

Table 4 presents radiotherapy guidelines for early breast cancer.

Table 4 Radiotherapy guidelines for early breast cancer

RT type	DCIS	OBC (T1/2; N0/1)	
		pT1/2 pN0	pT1/2 pN1
No RT required	Postmastectomy	(A) Highly select as per PRIME study criteria (grade 1–2, T1–T2 up to 3 cm especially in estrogen rich tumors)	X
Tumor bed + margins after BCT	After BCT in almost all cases unless the tumor low grade and ER positive allowing for endocrine prophylaxis	(B) APBI in select cases (ESTRO low and intermediate risk groups) (C) Boost in all cases except small low grade tumors in elderly as in EORTC trial	In all cases
Whole breast after BCS	For all patients	In all cases except (A) and (B)	In all cases
Chest wall after MRM	X	Under clinical trial setting	In all cases except select pN1 cases like grade 1 with T1 disease
Supraclavicular fossa	X	X	In all cases except select pN1 cases like grade 1 with T1 disease
Axilla	X	X	If SNB/AS positive and axilla not cleared
Internal mammary	X	X	X

6.6 Role of Radiation Therapy in Metastatic Breast Cancer

6.6.1 Bone Metastases (BM)

Radiation therapy provides effective palliation in majority of the patients of painful bone metastases with few side-effects [73]. Patients experience an improvement in their QoL, reduced analgesic requirements and maintenance or amelioration of skeletal function. Numerous studies have proven that single-fraction radiation therapy (SFRT) is equally effective for pain control and fracture risk as compared to multiple fraction palliative RT. Therefore, SFRT appears to be a more convenient fractionation as it reduces the treatment and travel time. However, patients undergoing SFRT have a higher retreatment rate which has to be discussed with the patient expected to have longer survival [74].

6.6.2 Brain Metastases (Brm)

Stereotactic radiosurgery (SRS) is an established noninvasive ablative therapy for patients having limited number (1–5) of brain metastases with a cumulative volume up to 20 cm^3. Randomized studies evaluating the role of SRS alone versus WBRT with SRS have shown no difference in the overall survival while those who received WBRT + SRS had greater cognitive decline and poor quality of life [75]. SRS alone has been shown to have higher local and distant brain failure (30%–70%) which may be treated with multiple sessions of SRS or salvage WBRT [63]. A meta-analysis favored treatment of younger patients (≤50 years) with SRS in view of better survival [76]. Treatment with SRS is technically challenging and coupled with a rigorous imaging follow-up schedule to detect new sites of metastases early for appropriate salvage therapies. SRS can be offered preoperatively or postoperatively as the only study that compared the two approaches did not find a difference in the survival end points. However, postoperative SRS had significantly higher rates of leptomeningeal disease, radiation necrosis and symptomatic radiation necrosis complications [77]. However, WBRT should be offered to patients having extensive disease and in patients with limited life expectancy.

Systemic Therapy

Multiagent chemotherapy is an important modality of care to improve outcomes. The benefit of adjuvant chemotherapy (ACT) is proven for both high-risk (high grade, lymph node positive) as well as lower-risk patient population [78].

The 2012 EBCTCG meta-analysis demonstrated efficacy of adjuvant chemotherapy and tamoxifen in reducing the risk of recurrence and mortality across all the age groups [79].

7 Regimen Selection and Administration

The choice of a regimen depends on both patient characteristics as well as disease biology. The standard of care is anthracycline-taxane-based therapy. As per the 2012 EBCTCG meta-analysis, AC is at least equivalent to an alternative nonanthracycline-based regimen, CMF [78]. Taxanes in addition to anthracycline-based chemotherapy improved outcomes, including recurrence, and cause specific and overall mortality. The increment was irrespective of age, tumor size, tumor grade, nodal positivity and estrogen receptor (ER) positivity [69]. Furthermore, sequential treatment with anthracycline-based regimen followed by taxanes (e.g., AC then T) was associated with improved outcomes [80].

"Dose-dense" adjuvant treatment, in which treatment is given more frequently than the historical 3-week schedule, is associated with better DFS outcomes, shortened cumulative time of treatment and similar tolerability compared with standard dosing. It is typically administered on an every week or every 2-week schedule [81].

The institutional standard regimen for most patients who require chemotherapy is doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T), sometimes known as AC-T. In high-risk and fit patients, it is given on a dose-dense schedule [81].

In women with endocrine-positive, HER2-negative, axillary node-negative disease, who had a low (10) and intermediate (11–25) 21-gene recurrence score (RS), adjuvant endocrine therapy with or without systemic chemotherapy had similar results. However, there was a small benefit of chemotherapy noted in women with 50 years of age or younger with a recurrence score of 16 to 25 [82].

Table 5 is a summary of adjuvant chemotherapy trials, and Table 6 presents recommended adjuvant chemotherapy regimens.

7.1 Neoadjuvant Systemic Therapy

Most patients with locally advanced breast cancer (LABC) need neoadjuvant systemic therapy to induce a tumor response before surgery and enable breast conservation. Regimens that are suggested for adjuvant treatment can also be employed in the neoadjuvant setting.

In the neoadjuvant context, the following approach may be recommended.

- Current research suggests that patients with hormone receptor-positive LABC should get neoadjuvant chemotherapy (NACT) rather than endocrine treatment to attain higher response rates in a shorter span.

Table 5 Summary of adjuvant chemotherapy trials

Comparison (reference)	Number of patients	Median follow-up (years)	Nodal status	Hazard ratio for disease-free survival	Hazard ratio for overall survival
CMF vs. no chemo [4]	386	28.5	Positive	0.71 ($P = 0.005$)	0.79 ($P = 0.04$)
CMF + Tam vs. Tam (B20)[5]	2306	5	Negative	0.65 ($P = 0.001$)	0.64 ($P = 0.03$)
AC vs. CMF (B15) [6]	2194	3	Positive	$P = 0.5$[a]	$P = 0.8$[a]
AC vs. CMF (B23) [7]	2008	5	Negative	$P = 0.9$[a]	$P = 0.4$[a]
FEC50 + Tam vs. Tam [8]	457	9.4	Positive	0.46 ($P = 0.0008$)	0.65 ($P = 0.07$)
FEC100 vs. FEC50 [9]	546	5.6	Positive	0.63 ($P = 0.02$)	0.45 ($P = 0.005$)
DCx4 vs. ACx4 [10]	1016	7	0–3 Positive	0.74 ($P = 0.033$)	0.69 ($P = 0.032$)
DAC vs. FAC [11]	1491	10.3	Positive	0.80 ($P = 0.004$)	0.74 ($P = 0.002$)
DAC vs. FAC [12]	1060	6.4	Negative	0.68 ($P = 0.01$)	0.76 ($P = 0.29$)
FAC-weekly T vs. FAC [14]	1925	5.3	Negative	0.73 ($P = 0.04$)	0.79 ($P = 0.31$)
FAC-weekly T vs. FAC [14]	2005	5.8	Positive	0.80 ($P = 0.01$)	0.85 ($P = 0.04$)
AC-T vs. AC-weekly T [15]	4954	12.1	Positive	0.84 ($P = 0.011$)	0.87 ($P = 0.09$)
AC-T vs. AC-D	5351	6.1	Positive	0.79 ($P = 0.001$	0.86 ($P = 0.054$)
AC-D vs. DAC [16]				0.83 ($P = 0.01$)	0.86 ($P = 0.09$)
AC-D vs. AD				0.80 ($P = 0.001$)	0.83 ($P = 0.03$)

AC doxorubicin, cyclophosphamide, *CMF* cyclophosphamide, methotrexate, 5-Fluorouracil, *DC* docetaxel, cyclophosphamide, *FAC* 5-Fluorouracil, doxorubicin, cyclophosphamide, *DAC* docetaxel, doxorubicin, cyclophosphamide, *FEC50* 5-Fluorouracil, epirubicin (50 mg/m^2), cyclophosphamide, *FEC100* 5-Fluorouracil, epirubicin (100 mg/m^2), cyclophosphamide, *D* docetaxel, *E* epirubicin, *T* paclitaxel

[a] Hazard ratios were not reported in the manuscript; however, *P* values did not reveal any statistical significance between study arms

Table 6 Recommended adjuvant chemotherapy regimens

Recurrence risk category	ER-positive, HER2-negative	ER/PR-negative, HER2-negative	HER2-positive
Very low risk			
• Node-Neg, T1a	No chemotherapy	No chemotherapy	No chemotherapy
Low risk			
• Node-Neg, T1b	DCx4 or ACx4 (ifRS is high)	DCx4 or ACx4	Weekly paclitaxel + H
• Node-Neg, T1c	DCx4 or ACx4 (if RS is high or mid-range with age <50)	DCx4 or ACx4	Weekly paclitaxel + H or TCH
Moderate risk			
• Node-Neg, T2	DCx4 or ACx4 or AC-T (ifRS—high range or mid-range with age <50)	AC-T	AC-T + H or TCH ± P
High risk			
• 1+ Posnodes or T3	AC-T	AC-T	AC-T + H or TCH ± P

AC doxorubicin, cyclophosphamide, *T* paclitaxel, *H* trastuzumab, *P* pertuzumab, *TCH* docetaxel, carboplatin, trastuzumab, *Neg* negative, *Pos* positive, *RS* recurrence score

- An anti HER2 therapy (e.g., trastuzumab with or without pertuzumab) merits to be added to the chemotherapy regimen for patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

Patients either complete entire chemotherapy as NACT or may receive NACT and adjuvant chemotherapy (ACT) both depending upon institutional practice.

According to the CREATE-X trial, women with residual disease following standard NACT may be appropriate candidates for adjuvant capecitabine for triple-negative breast cancer [83].

7.2 Anti-HER2-Targeted Therapy

Patients with malignancies that overexpress HER2 benefit from anti-HER2 therapy. A 2012 meta-analysis of chemotherapy plus trastuzumab versus chemotherapy alone found that adding trastuzumab to ACT improved disease-free survival (DFS) and overall survival (OS) in patients with HER2-positive disease [84].

Women with either node-positive or node-negative high-risk disease (generally defined as tumor size >1 cm were included in the majority of trials demonstrating the efficacy of adjuvant trastuzumab [85].

In a single-arm trial, the benefit of adjuvant trastuzumab plus paclitaxel (anthracycline-free regimen) in patients with low tumor burden HER2-positive tumors was investigated, and 3-year recurrence-free survival rates of around 99% were found [86].

Based on the phase III APHINITY trial, adjuvant pertuzumab for a year may be considered for the high-risk patients with either node-positive disease or node-negative tumors with >2 cm size to improve disease-free survival [87].

Administration of trastuzumab sequentially after completion of all chemotherapy has demonstrated activity but it appears to be less effective than when given concurrently.

We recommend endocrine therapy concurrently with trastuzumab during maintenance treatment (following completion of adjuvant chemotherapy).

The 2012 meta-analysis suggests that trastuzumab should be given for 1 year with adjuvant chemotherapy rather than for shorter periods [84]. Subsequent trials reaffirm this recommendation and also demonstrate no improvement with extension to 2 years [13]. We advocate 1 year of trastuzumab in patients with either node-positive disease or with hormone receptor-negative disease. We suggest a shorter duration of adjuvant trastuzumab (6 months duration) in patients with low risk of disease (defined as node-negative, triple-positive disease) based on a recent meta-analysis done at our center [88].

Patients who received NACT should get trastuzumab in the adjuvant setting to complete a full year of trastuzumab therapy, accounting for the number of cycles of trastuzumab given in both the neoadjuvant and adjuvant settings. Continue pertuzumab with trastuzumab in the adjuvant situation for patients who received neoadjuvant pertuzumab.

7.3 Endocrine Therapy

Patients with malignancies that are hormone receptor-positive (ER, PR, or both) benefit from adjuvant endocrine therapy. The choice of endocrine therapy depends on the menopausal status of the patient. The various endocrine therapies are as follows:

Premenopausal patient

Tamoxifen alone

Tamoxifen with ovarian suppression or ablation—that can be achieved by Surgery (oophorectomy), Pelvic radiation (ovarian ablation), Gonadotropin-releasing hormone (GnRH) agonists.

Tamoxifen—a 2011 EBCTCG meta-analysis compared 5 years of tamoxifen treatment to no endocrine treatment and found a significant reduction in the risk of breast cancer recurrence and mortality at 15 years [89].

Postmenopausal patient—Aromatase inhibitors (AI)—Aromatase is a key enzyme in the conversion of androstenedione to estrogen in peripheral fat tissue and by inhibiting this enzyme. AI block the peripheral conversion of androgen to estrogen. Since this mechanism is predominantly active in postmenopausal woman, AIs are recommended there and not for premenopausal and/or women with chemotherapy-induced amenorrhea. The efficacy among the AIs is comparable [90] and in comparison to tamoxifen, AIs fared better in reducing recurrence risk during therapy and reducing breast cancer mortality both during and after treatment [78].

7.3.1 Premenopausal Women: Choice of Tamoxifen Alone vs. Tamoxifen with OFS

Based on the results of the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT), we recommend Tamoxifen in combination with ovarian function suppression (OFS) rather than tamoxifen alone for women with high-risk breast cancer, inclusive of age ≤35 years, large tumor size, presence of pathologically involved lymph nodes, high tumor grade, lymphovascular invasion and/or high risk of recurrence based on a genomic assay [91].

Tamoxifen is a choice as a single agent to women with low risk of recurrence.

7.3.2 Postmenopausal Women

We perennially use an AI for the postmenopausal breast cancer women in view of superior DFS. However, both agents reduce recurrences and new primary breast cancers and one should be cognizant about the potential toxicities while selecting endocrine therapy.

Adjuvant endocrine therapy is administered for at least 5 years. Unless there is a contraindication to continued endocrine therapy, all patients should receive adjuvant endocrine therapy for at least 5 years (such as prior thrombosis on tamoxifen or osteoporosis refractory to bone-modifying agents). In high-risk women, extended therapy for 10 years is recommended.

8 Metastatic Breast Cancer

In the following circumstances, cytotoxic chemotherapy may be used: (1) hormone receptor-negative breast cancer; (2) hormone receptor-positive breast cancer that has progressed after multiple lines endocrine agents (i.e., endocrine-resistant disease) or has a significant tumor burden including visceral organs.

8.1 Choice of Chemotherapy

Multiple criteria, including tumor burden, ECOG performance status, prior therapies potential toxicities and patient desire, influence the choice of regimen (i.e., single agent or combination) and specific therapy for patients who require chemotherapy. Single-agent chemotherapy is preferred for patients with a small tumor burden. Sequential monotherapy is equally efficacious and less toxic to multiagent therapy and is preferred [92]. A combination regimen is preferred for a small, select subgroup with either frank or imminent visceral crisis; they are usually having a substantial tumor burden (extensive liver metastases or dyspnea related to diffuse lung metastases).

8.2 Duration of Treatment

Duration of chemotherapy should be guided by the patient's performance status, existing and potential toxicities, and access to alternative choices. Patients should continue chemotherapy until they have the optimal response, progressive disease, or unacceptable side effects. There is some evidence to show that extending treatment beyond their best response has benefits. Maintenance treatment was compared to treatment for a predetermined time (range, three to eight cycles) in a meta-analysis of randomized studies [93]. Progression-free survival (HR 0.64, 95% CI 0.55–0.76) and overall survival improved (HR 0.91, 95% CI 0.84–0.99) with longer treatment duration of paclitaxel and gemcitabine in a randomized trial [94].

9 HER2-Positive MBC

9.1 First-Line Therapy

9.1.1 Trastuzumab

Slamon et al. [95] provided the first definitive evidence of anti-HER2-targeted therapy in a clinical trial where in treatment naïve metastatic hER-2-positive patients were administered chemotherapy with or without trastuzumab. The combination of chemotherapy and trastuzumab resulted in a significantly superior outcomes including higher objective response rate, longer time to progression (TTP; 7.4 vs. 4.6 months; $p<0.001$) and enhanced overall survival (OS; 25 vs. 20 months; $p = 0.01$).

9.1.2 Lapatinib

Chemotherapy with or without lapatinib was tested in a randomized trial, wherein OS was 20.7 months in the combination arm versus 20.5 months in the chemotherapy alone arm [96]. Lapatinib and trastuzumab with taxane were examined in the MA.31 study, and PFS was observed to be poorer with lapatinib (8.8 months vs. 11.4 months with trastuzumab) at the interim analysis [97]. At present, based on the foregoing findings, trastuzumab-based regimens are the standard of care in first-line situations.

9.1.3 Trastuzumab Plus Pertuzumab

The Cleopatra trial [98] investigated adding pertuzumab to standard taxane and trastuzumab therapy and demonstrated superiority of pertuzumab with respect to OS (56.5 months in pertuzumab arm vs. 40.8 months with placebo) at a median follow-up of 50 months.

9.2 Second-Line Therapy

There is phase III randomized evidence to continue anti-HER2 therapy in patients whose disease has progressed on first-line trastuzumab-based therapy with alternating chemotherapy regimen. Treatment options include changing to the antibody drug conjugate T-DM1, adding the mTOR pathway inhibitor everolimus, changing to a Capecitabine plus lapatinib regimen.

10 Hormone Receptor-Positive Metastatic Breast Cancer

Endocrine therapy (ET) is preferred option unless there is clinically severe disease that requires a faster response or endocrine resistance. There are various determinants including menopausal status, comorbidities and drugs given in the adjuvant setting in deciding which endocrine agent to use. The sequential use of endocrine therapy—tamoxifen, Aromatase inhibitors and Fulvestrant—has been the main stay of treatment since years. In last few years, introduction of newer targeted therapies (like CDK4/6 inhibitors, PI3K inhibitors) have provided non-chemotherapy-based options which have improved the outcome of hormone receptor-positive metastatic breast cancer patients. The effectiveness of CDK4/6 inhibitors in combination with endocrine therapy has been confirmed in multiple phase III studies and is now the preferred first-line treatment [99–101]. Around 40% of patients have activating mutations in PI3KCA, and use of alpelisib along with fulvestrant in these patients has shown improved PFS compared to hormonal therapy alone [102].

11 Special Scenarios

11.1 Young Women with Breast Cancer

Recent data from Tata Memorial Centre in large cohorts of young breast cancers (YBC) defined as ≤40 years of age (*N* = 1228) suggest that they represent higher percentage of total BC (16.7%) then in the west. Furthermore, in this study Bajpai et al. [103] demonstrated that a large majority are diagnosed at an advanced stage due to multitude of reasons including delayed diagnosis and/or referral. They are of higher stage, grade, node positives and predominantly TNBC and HER2 positives. There were unique concerns regarding significant postmenopausal symptoms post treatment and concerns regarding fertility preservation. A small fraction of YBC could conceive and successfully deliver live babies post successful treatment of breast cancer.

YBC women have challenges associated with body image, including chemotherapy induced alopecia which can be circumvented via scalp cooling devices. A randomized controlled trial by Bajpai et al. [104] has shown success with regard to alopecia prevention as well as hair regrowth. Yet another study from the institute by Bajpai et al. showed in a large cohort of nonmetastatic TNBC that they present in an advanced stage and had aggressive clinicopathological features which adversely affects outcomes. Pregnancy associated breast cancer (PABC) is a unique entity and encompasses two entities breast cancer diagnosed during pregnancy (BCP) or 1-year postpartum (BCPP). Bajpai et al. [105] in the first Indian PABC registry demonstrated the prevalent delayed diagnosis and again aggressive clinicopathological features including TNBC and higher grades and stage. Stage and biology matched outcomes of PABC were comparable to non-PABC and those of YBC and TNBC with published literature.

11.2 Palpable DCIS (pDCIS)

pDCIS has a 10% to 14% risk of harboring an invasive component. It is essential to differentiate microinvasive DCIS from multiple foci of invasive ductal carcinoma (IDC) [106] in a background of DCIS with extensive intraductal component (EIC). The pathologist's role is critical in defining the same.

The incidence of axillary lymph node metastases with DCIS is only 1.4%, while with DCIS-M, it is higher at 5.1% [107]. Possible indications for axillary lymph node dissection are the suspicion of microinvasion, such as the presence of a clinically palpable node or palpable comedo-type DCIS. Due to the underestimation of invasion in biopsies of pDCIS, lymphatic mapping using sentinel lymph node biopsy or axillary sampling at the time of surgery, with both modified radical mastectomy and breast-conserving procedure may be considered [108]. The role of adjuvant therapy in pDCIS and DCIS-M is still not clear.

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Non-Small Cell Lung Cancer

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Abbreviations

AJCC	American Joint Commission on Cancer
ALK	Anaplastic lymphoma kinase
DLCO	Diffusion coefficient of carbon monoxide
EBUS	Endobronchial ultrasound
EGFR	Epidermal growth factor receptor
EUS	Endoscopic ultrasound
FDA	Food and Drug Administration
IASLC	International Association for the Study of Lung Cancer
IGRT	Image-guided radiation therapy
IMRT	Intensity modulated RT
IPPB	Intermittent positive pressure breathing
NACT	Neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
PD-1	Programmed cell death receptor
PD-L1	Programmed cell death ligand
PORT	Postoperative RT
RT	Radiotherapy
SABR	Stereotactic ablative radiation therapy
SBRT	Stereotactic body radiotherapy
SCLC	Small cell lung cancer
SMLND	Systematic mediastinal lymph node sampling
TKI	Tyrosine kinase inhibitor
VAM	Video-assisted mediastinoscopy
VATS	Video-assisted thoracoscopic surgery
V/Q	Ventilation-perfusion

1 Introduction

Lung cancer is the most frequently diagnosed cancer worldwide and is a major health problem in both developed and developing countries in the world. Lung cancer is the most common cause of death in both men and women. Survival is generally poor with only less than 10% of patients remaining alive at 5 years after diagnosis [1]. Smoking is the main risk factor for lung cancer in developed countries, accounting for 80–90% of cases. About 10–15% of cases occur in non-smokers, and these may often be caused by a combination of genetic factors and exposure to environmental hazards like radon gas, asbestos, second-hand smoke, or other forms of air pollution [2–4].

Lung cancer is divided into two main types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Although the etio-pathogenesis is similar, treatment principles are different for each of these types. NSCLC is a heterogeneous aggregate of different histologies. The most common histologies are squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma. These histologies are often classified together because approaches to diagnosis, staging, prognosis, and treatment are similar. Generally, treatment involves a multidisciplinary approach with surgery, systemic therapy, and radiation therapy used in various combinations.

2 Incidence and Epidemiology

Lung cancer occurred in approximately 1.8 million patients worldwide in 2012 and caused an estimated 1.6 million deaths. Lung cancer is known to account for more deaths than any other type of cancer.

In India, as per GLOBOCAN 2012 report, the estimated incidence of lung cancer was more than 70,000 cases across all ages and sexes; the age-standardized rate (ASR) per 100,000 was 6.9, with a cumulative risk of 0.85. Incidence of lung cancer ranked fourth overall among the various types of cancer behind breast, cervical and oral cavity cancer, ranking

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second in males and seventh in females. In Indian males, lung cancer had a crude incidence rate of 8.3, ASR of 11 and cumulative risk of 1.36; in Indian females, crude incidence rate was 2.7, ASR 3.1 and cumulative risk 0.37. Lung cancer was the third most common cause of cancer-related deaths in India after breast and cervical cancer. Among Indian males, lung cancer was the leading cause of cancer mortality and among Indian females seventh after breast, cervix, colorectal, ovary, stomach and oral cavity cancers. It is also estimated that by 2025, the incidence of lung cancer would increase to more than 1 lakh and the mortality to 92,601. It is expected that lung cancer will remain a major health problem at least for the next three to four decades, even if smoking cessation interventions lead to a reduction in incidence [5–8].

Tobacco smoking remains the single most important risk factor (80–90%) for lung cancer with a smaller proportion (10–20%) attributable to occupational exposure to various carcinogenic agents. Comparatively, the smoker-non-smoker ratios have been low in Indian studies compared to those from the West. The percentage of tobacco-related products smoked in India are beedis (28.4–79%), cigarettes (9.0–53.7), hookah (3.4–77.3) and mixed (7.5–13.6). The relative risk of developing lung cancer varies according to the type of tobacco smoking; 2.64 for beedi smokers, 2.23 for cigarette smokers and 2.45 as the overall risk for smoking tobacco. Passive, second-hand smoking and environmental tobacco smoke are also known lung carcinogens. The risk also increases with an increase in the number of smokers in the house and the duration of exposure. Childhood exposure to environmental tobacco smoke is strongly associated with the risk of developing lung cancer [9, 10].

In the Western countries and most of the Asian countries, adenocarcinoma has surpassed squamous cell carcinoma as the leading histologic variant of lung cancer. This shift can be partly attributed to the changing smoking pattern and increasing incidence of lung cancer in women and non-smokers. However, most of the older and some recent Indian series report that squamous cell carcinoma continues to be the most common histology. However, single-center-based reporting from the established tertiary cancer centers point toward adenocarcinoma being the most common NSCLC subtype.

Occupational exposure leading to lung cancer is definitely linked with workers exposed to asbestos, arsenic, nickel, chromium, beryllium, silica, chloro-methyl ether, mustard gas and radiation from uranium, radon; while agents like acrylonitrile, cadmium, formaldehyde and vinyl chloride are suspected to be carcinogenic [11].

There is a genetic component in the carcinogenesis of lung cancer both with regard to host susceptibility, with or without exposure to tobacco smoke to the development of malignancy and to an individual's responsiveness to biologic therapies. Polymorphisms in genes associated with DNA repair enzymes active in base excision repair (XRCC1 and OGG1), nucleotide excision repair (ERCC1, XPD, and XPA) and double strand break repair (XRCC3), and different mismatch repair pathways have been linked to lung cancer risk. Several of these cancer susceptibility genes have been associated with increased levels of DNA adducts; additionally acquired or epigenetic changes in DNA chromosome like DNA methylation, histone de-acetylation and phosphorylation can also lead to increased lung cancer risk [12]. Despite many genetic association studies, the role of specific genes in increased risk for lung cancer remain poorly understood.

The high morbidity, mortality associated with NSCLC, and relative high prevalence in high-risk population make it an appropriate disease for screening. Since mortality and survival are related to the stage at diagnosis, early detection may be beneficial. Many randomized controlled trials in the western world have shown reduced lung cancer specific and all-cause mortality by screening with low-dose CT scan LDCT in patients with personal smoking exposure. According to the U.S. Preventive Services Task Force, annual screening for lung cancer with low-dose CT is recommended in adults aged 55–80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years [13, 14]. However, the enormous financial burden of the screening programmes in existing health-care system and lack of uniform accessibility to diagnostic modalities are major road blocks for implementing a successful screening programme in India [15].

3 Clinical Presentation

Initial clinical presentation in lung cancer could be a manifestation of the local disease, loco regional spread, extra thoracic spread (distant metastases) or due to paraneoplastic syndrome. Cough occurs in 70–90% of patients with lung cancer and may be produced either by small tumour interfering with bronchial peristalsis or by ulceration of bronchial mucosa. Cough and sputum production may be nonspecific, as cigarette smoking also produces bronchorrhea and excessive mucus. Peripheral tumours may also attain large size without producing cough. Severe bouts of cough can also result in pneumothorax due to rupture of an emphysematous bleb, fainting (cough syncope) or even rib fracture.

Hemoptysis is a common symptom occurring in 25–40% of patients. It may be due to ulceration of the bronchial mucosa by tumour or related to rupture of bronchial veins or venules leading to significant loss of blood. Breathlessness is also an early symptom occurring in about 60% of patients. It may be disproportionate to radiological findings due to associated underlying smoke-related lung changes. Wheezing, stridor or sudden increase in breathlessness is highly suggestive of a partial bronchial obstruction and may result from pressure and narrowing of large bronchus or trachea.

Chest pain is also a common symptom in lung cancer and may be present without frank evidence of invasion of the pleura, chest wall or mediastinum. Since lung parenchyma lacks pain fibres, the origin of this type of pain is sometimes vague. Pleural metastasis may result in severe chest pain necessitating narcotics. Persistent chest pain with invasion of bony thorax is often caused by squamous cell carcinoma. Superior sulcus tumour often produces shoulder and arm pain because of invasion of brachial plexus (Pancoast syndrome). It can be accompanied by Horner's syndrome, brachial plexopathy and reflex sympathetic dystrophy.

Hoarseness of voice in association with lung cancer is caused by involvement of the recurrent laryngeal nerve. The phrenic nerve can be invaded by the primary tumour or bulky adenopathy. The left recurrent laryngeal and phrenic nerve are more commonly affected than the right. Dysphagia can result from oesophageal obstruction by bulky mediastinal adenopathy or recurrent laryngeal nerve injury. Superior vena cava syndrome is a common complication of lung cancer and a consequence of obstruction of superior vena cava by right upper lobe or hilar tumour. The syndrome is characterized by facial swelling, flushing, and neck and chest wall vein distention.

Approximately 15–20% of lung cancer patients present with pleural effusion. Pericardial effusion develops in 5–10% of patients and typically occurs in the setting of progressive locally advanced disease [16, 17].

Patients with advanced disease can present with symptoms specific to site of distant metastases. Most common sites of metastases include brain, bone, adrenals and liver. The manifestations of brain metastasis are variable and depend on the location of the lesion and the amount of the associated oedema or haemorrhage. Patient may present with focal weakness, generalized or focal seizures, confusion or dementia, dysphasia, visual disturbances, or ataxia. Leptomeningeal disease may present as cranial nerve palsies or cauda equine syndrome. Bone is a commonly involved site of metastases; patient may present with significant bone pain requiring narcotics or neurological deficits secondary to compression syndromes.

Patients with paraneoplastic syndromes, secondary to systemic manifestations of lung cancer, could present with endocrinological, neurologic, musculoskeletal, haematological or dermatological abnormalities.

In around 5% of patients, lung cancer may be discovered incidentally during the investigation of an unrelated complaint, or on a chest radiograph done as part of a pre-operative evaluation or as part of an extended physical examination [16].

4 Evaluation and Work-Up

Given the importance of staging in decision-making process, a thorough staging workup for NSCLC should be carried out to evaluate the extent of disease. A complete metastatic workup is indicated in all patients with potentially operable NSCLC and in those who can be offered radical therapy such as concurrent chemo radiation with a curative intent. Pre-treatment workup includes:

1. Chest X-ray
2. CT scan chest and upper abdomen
3. Fibre optic bronchoscopy
4. Cytology/histological diagnosis—sputum cytology, broncho-alveolar lavage/brushings cytology, post bronchoscopy sputum cytology, CT-guided biopsy
5. Pulmonary function test and diffusion coefficient of carbon monoxide (DLCO)
6. Ventilation-perfusion (V/Q) scan—if pulmonary function tests reveal borderline pulmonary reserve
7. Resting 2D ECHO/Stress 2D ECHO may be performed to assess cardiac status in patients planned for major resections or have pre-existing cardiac co-morbidity
8. Invasive mediastinal staging is indicated in all patients with potentially operable NSCLC. Peripherally located T1a squamous cancers with negative mediastinal imaging on PET-CECT may be excluded. If available, combined EUS/EBUS with guided FNAC is the preferred initial staging modality. All negative EBUS studies should be confirmed by video-assisted mediastinoscopy (VAM)
9. Metastatic workup—PET-CT scan, MRI brain—indicated in all patients with non-metastatic NSCLC fit for radical treatment. Patients with T1 (T <10 mm), N0 NSCLC with no symptoms of metastatic disease do not require a routine metastatic workup.

Histopathological diagnosis of NSCLC includes squamous cell carcinoma (25–30%), adenocarcinoma (35–40%) and large cell carcinoma (10–15%). Various IHC markers may aid in differentiation between the types (Table 1).

Table 1 NSCLC histopathology

Histology	IHC markers
Squamous cell carcinoma	Cytokeratin (CK) cocktail—AE1/AE3 CK5/6 CK7 (rare)
Adenocarcinoma	Cytokeratin cocktail—AE1/AE3 CK7, TTF-1 Neuroendocrine markers—CD56, NSE (rare)
Large-cell carcinoma	Cytokeratin, TTF-1 rare Neuroendocrine markers—CD56, NSE (rare)

Cervical mediastinoscopy remains the gold standard for staging the mediastinum and should be done in all patients planned for surgical excision. Endoscopic ultrasound (EUS) and endobronchial ultrasound (EBUS) guided fine needle aspiration cytology can be used for initial staging where the expertise is available, but in case of negative staging, invasive staging with mediastinoscopy is required.

Pre-operative pulmonary evaluation tests are done to assess adequacy of pulmonary reserve prior to definitive treatment including lung surgery or chemoradiation. This includes spirometer, 6-min walk test, shuttle test and other cardio-pulmonary exercise testing.

Pre-treatment identification and treatment of concomitant risk factors are also vital. This may include management of smoking cessation, co-existing pulmonary disease with bronchodilators, intermittent positive pressure breathing (IPPB), chest physiotherapy and antibiotics (if presence of infection is suspected).

The eighth edition of the American Joint Commission on Cancer (AJCC) TNM staging system for non–small cell lung cancer [18] was introduced in January 2017 and implemented from January 2018 Staging can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 447–448, Chapter no. 36, Lung, Table: Definition of TNM and AJCC prognostic stage groups which can be accessed at https://emedicine.medscape.com/article/2007813-overview.

The eighth edition of the TNM staging system is based on the recommendations of the International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee (SPFC) [19]. The main purpose of stage classification is to provide a uniform nomenclature about the anatomic extent of disease that can be used consistently globally.

4.1 Predictive and Prognostic Biomarkers

Several predictive and prognostic biomarkers have emerged for NSCLC. Key established predictive biomarkers include sensitizing EGFR mutations, ALK rearrangements, ROS1 rearrangements, BRAF V600E point mutations and PD-L1 expression levels. Emerging biomarkers include HER2 mutations, RET rearrangements, MET amplification and MET exon 14 skipping mutations [20].

In all NSCLC patients with an element of adenocarcinoma, regardless of the clinical profile, genomic testing for EGFR and ALK alterations as a part of the standard diagnostic evaluation is recommended. . The National Comprehensive Cancer Network (NCCN) extends the recommendations for metastatic NSCLC to include BRAF, ERBB2 (HER2), MET, RET and ROS1 [21].

Epidermal growth factor receptor is a cell signalling, transmembrane protein intimately involved in proliferation. Mutations can occur in the kinase region leading to unregulated phosphorylation and activation of cell survival/proliferation pathways. The incidence of EGFR mutation is the highest in non-smokers, female gender with adenocarcinoma. Of all the various EGFR gene known mutations in lung adenocarcinoma, 90% are of exon 19 and L858R point mutation in exon 21. These mutations are more frequent in Asian populations with its frequency reaching 60% as compared to 10% in US populations [22–25].

The echinoderm microtubule associated protein-like 4 (EML)-anaplastic lymphoma kinase (EML4-ALK) protein results from the fusion of PTK EML-4 with ALK, a transmembrane tyrosine kinase. The resulting constitutive oligomerization leads to persistent mitogenic signalling and malignant transformation. ALK mutation is reported in approximately 3–7% of lung cancers, seen more frequently in young, non-smoking adults with adenocarcinoma histology. In the majority of patients, ALK rearrangements are exclusive and do not overlap with other oncogenic mutations [26–28]. ROS1 gene promotes proliferation and inhibits apoptosis; mutations are seen in 1–2% of all NSCLC patients through a rearrangement that leads to unregulated production of fusion proteins which retain the kinase domain.

5 Principles of Management (An Integrated Brief Overview of RX Philosophy)

All patients should be preferably discussed in a multidisciplinary tumour board meeting including specialists from surgical oncology, radiation oncology, medical oncology, radiology, bio-imaging, pulmonologist and palliative care departments. Ancillary support care may be provided by psychiatrists, occupational and physiotherapists.

Treatment for NSCLC is planned according to the clinico-radiological stage, cardio-pulmonary reserve and performance status. Patients should be treated in concordance with standard consensus guidelines, including institutional evidence-based medicine.

5.1 Localized (T1-3, N0-1) Non-Small Cell Lung Cancer (NSCLC)

Surgical resection is the cornerstone in the treatment of early-stage NSCLC. Invasive mediastinal staging should be performed on all patients planned for surgical excision. Lobectomy or pneumonectomy along with N1 and N2 lymph nodal resection and mapping (sampling or systematic lymph node dissection) is done depending on the extent of disease (provided the patient has adequate pulmonary reserve). Limited resections (segmentectomy, wedge resection) may be done only if pulmonary reserve is inadequate for lobectomy, provided otherwise medically fit for surgery. Curative SBRT or radical radiotherapy may be administered if the patient is medically unfit for surgery. All resected NSCLC (T size >4 cm) or any node positive (N1 or more) receive adjuvant cisplatin-based chemotherapy. Postoperative radiation may be indicated in the presence of positive margins, pathological N2 disease or residual disease. Patients with pre-operative diagnosis of N2 disease undergo neoadjuvant chemotherapy followed by surgery. Patients progressing on neoadjuvant chemotherapy are treated with definitive chemoradiotherapy.

5.2 Loco-Regionally Advanced (T4 and N3) NSCLC

Patients with unresectable NSCLC in good general condition are managed with combined chemoradiotherapy. Patients who may not tolerate combination therapy are treated with radiotherapy alone.

Patients with metastatic lung cancer are treated with systemic therapy, which may include chemotherapy, targeted therapy or immunotherapy. Symptomatic bone, brain and soft tissue metastases may be palliated with radiation therapy. Patients in poor general who are unfit for any form of tumour-directed therapy are given best supportive care.

6 Surgical Management

6.1 Early-Stage NSCLC

Early-stage NSCLC (stage I and stage II) are generally treated with surgery as the initial modality. Resection of the primary tumour and evaluation of draining lymph nodes in the ipsilateral hilum and mediastinum are key aspects in surgery for early-stage NSCLC.

6.1.1 Primary Tumour Resection

Lobectomy is the current standard for resection in lung cancer. If the patient has adequate pulmonary reserve, lobectomy, bi-lobectomy or pneumonectomy should be done depending on the extent of disease. The large scale, ACOSOG Z0030 (ALLIANCE) trial, set the benchmark for surgical outcomes in early-stage NSCLC; with a median follow-up of 6.7 years, overall survival at 5 years was 72% for T1 tumours and 55% for T2 tumours [29]. Lung resections carry significant morbidity with up to 37% of patients experiencing minor or major postoperative morbidities. Minor complications are more common (atrial arrhythmia and prolonged air leak) while major complications like respiratory failure can occur in patients with poor baseline pulmonary function. The operative mortality following lobectomy is reported to be 1–3% in high volume surgical centres.

Video-assisted thoracoscopic surgery (VATS), typically involves two to four port sites and a 5–8 cm access incision. It involves removal of lung lobe containing the tumour with ligation of each of the broncho-vascular structures and removal of hilar and mediastinal lymph nodes. VATS differs from mini-thoracotomy by the lack of rib spreading and complete thoracoscopic visualization. In a propensity score matched analysis, no difference was observed in overall survival, disease-free survival and freedom from development of a new primary tumour between the two approaches [30]. However, most large series of VATS lobectomy report a similar pattern of perioperative complications but at significantly reduced rates as compared to the open approach. Another modern technological advancement, robotic lobectomy has multiple advantages including reduced pain at port site, and binocular visualization. Large, prospective studies with robust long-term oncologic outcomes are lacking; however, initial reports show comparable survival outcomes between the VATS and robotic approaches.

Sub-lobar resection refers to removal of less than a pulmonary lobe. Limited resection (segmentectomy, wedge resection) may be done only if pulmonary reserve is inadequate for lobectomy, provided otherwise medically fit for surgery. However, a randomized trial (LCSG) [31] and few other nonrandomized trials have demonstrated increased local recurrences and lower survivals with sub-lobar resections compared to lobectomy [32].

6.2 Nodal Evaluation and Resection

Evaluation of the draining lymph nodes provides valuable staging information and is an integral part of surgery for NSCLC. It can be done either pre-operatively or peroperatively. Endobronchial ultrasound and **c**ervical mediastinoscopy are pre-operative procedures for evaluating mediastinal lymph nodes for cancer involvement. Peroperatively, a systematic mediastinal lymph node sampling (SMLND) may be performed, where lymph nodes at each of the ipsilateral mediastinal station are biopsied (stations 2R, 4R, 7 and 9R on the right side and levels 5, 6, 7 and 9 L on the left), or by formal mediastinal lymphadenectomy wherein all nodes and soft tissue between anatomical landmarks are dissected.

Although the ACOSOG Z0030 trial did not demonstrate a benefit in overall survival with SMLND over sampling alone in node negative patients [29], an identical large randomized trial from China demonstrated a significant survival benefit with SMLND in operable NSCLC. Pooled analysis of four RCTs shows a trend toward improved survival with SMLND and none of these trials demonstrate any additional morbidity or mortality with SMLND [33].

6.3 Locally Advanced NSCLC (T1–3, N2)

Stage III NSCLC represents a heterogeneous group of malignancies with locoregional involvement by extension of the primary tumour and/or ipsilateral lymph node involvement. Stage IIIB/IIIC with N3 disease (supraclavicular and/or contralateral mediastinal lymph nodes) is not typically treated surgically. Surgical indications have not been definitely established for stage IIIA and are treated with a multimodality approach. The use of surgery in these treatment regimens is not universally accepted and should be tailored to individual case. Stage IIIA NSCLC patients fall into two classes: pre-operatively diagnosed N2 disease and surgically discovered N2 disease.

6.3.1 Pre-Operatively Diagnosed N2 Disease

Patients with clinico-radiological N2 disease should undergo mediastinoscopy for histological confirmation of N2 status. Outcomes in these patients with surgery as a sole treatment modality have been historically poor, with studies showing 5-year survival rates less than 10%. Therefore treatment strategies have evolved to include multimodality approaches. A large meta-analysis showed significant benefit to postoperative chemotherapy in this subset; however, there was a significant incidence of grade 3 or 4 toxicity events, and 33% of them could not complete the planned adjuvant therapy [34, 35].

Several studies have evaluated the impact of neoadjuvant chemo-irradiation, followed by surgery. In the Intergroup (INT) 0139, patients were treated with induction chemo-irradiation and then randomized between surgery or further radiotherapy [36]. In the ESPATUE phase III trial, patients received induction chemotherapy followed by chemo-irradiation and then surgery [37]. In the EORTC 08941 trial, patients responding to induction chemotherapy were randomized to surgery or radiotherapy [38]. All three trials showed that overall survival was not different between surgical and non-surgical arms, although progression-free survival was improved in the surgical group in the Intergroup trial. Also, mortality of patients undergoing complex, intra-pericardial pneumonectomies was unacceptably high. An unplanned sub-analysis showed significant survival difference in patients undergoing lobectomy after induction chemo-irradiation compared to a similar group treated by chemo-irradiation only. A recent meta-analysis including randomized trials comparing surgery with definitive radiation therapy demonstrated no difference in overall and progression-free survival between surgery and radiotherapy in the setting of stage III NSCLC [39]. Patients who progress on neoadjuvant chemotherapy are treated with definitive chemoradiotherapy. Since mediastinal nodal down-staging is an important prognostic factor, a thorough attempt to restage the mediastinum after induction therapy should be undertaken before embarking on any major surgical intervention.

6.3.2 Surgically Discovered N2 Disease

Patients who have not received pre-operative chemotherapy should be given postoperative chemotherapy (see below). The role of adjuvant radiotherapy in completely resected N2 NSCLC is debatable (see below). Subset analysis in the PORT meta-analysis showed no difference in survival [40]; however, a large SEER database analysis showed improvement in survival with postoperative radiation in patients with N2 disease [41].

7 Radiation Management

Radiotherapy (RT) is an essential modality in the management of NSCLC. RT is the primary treatment modality for locally advanced, unresectable disease and is usually delivered concurrently with chemotherapy. In postoperative setting, RT can used as an adjuvant treatment to improve locoregional control. Radiotherapy is also frequently used for the palliation of symptoms in advanced and metastatic lung cancer. RT for NSCLC is usually delivered using external-beam radiotherapy via a linear accelerator. Newer techniques, such as intensity modulated (IMRT) and image-guided radiation therapy (IGRT), have improved the therapeutic ration by reducing the toxicity profile and allowing for dose escalation.

7.1 Early-Stage NSCLC

Surgical resection is currently the standard treatment for the medically operable ES-NSCLC, with 10-year survival rates ranging from 45% to 75% [42]. However, about 20% of the patients with stage I NSCLC cannot or do not undergo surgery owing to poor pulmonary, cardiac function and perceived higher risk of mortality with surgery, especially in elderly patients [43]. Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiation therapy (SABR), typically involves the delivery of 1 or a few large-dose fractions of 8–30 Gy per fraction. Technological advances in image guidance and radiation treatment delivery techniques have enabled the delivery of high doses to targets with tighter margins and high gradients outside the target, thereby minimizing doses to surrounding normal tissues. SBRT utilizes smaller margins for set-up uncertainty, aided by 4-dimensional computed tomography (4DCT), multiple conformal or intensity modulated beams or arcs and volumetric image guidance.

Several long-term retrospective series, phase II and III studies have evaluated SBRT in medically inoperable ES-NSCLC and shown 5-year local control rates ranging between 73% and 92% and overall survival (OS) of 50–70% [44–46]. Various total dose and fractionation schedules have been utilized in the past; the overall dose delivered to the tumour is strongly associated with local control. In a retrospective review, Onishi et al. analysed a variety of dose fractionation schedules and showed that local control and survival were significantly improved with BED_{10Gy} greater than 100 Gy, with 5-year local recurrence rate of 8% for $BED_{10Gy} > 100Gy$ versus 26.4% for $BED_{10Gy} < 100Gy$ ($p < 0.001$) [47].

Dose fractionation is also determined based on the location of the primary disease. In patients with central tumours undergoing SBRT, a pivotal phase II study reported that a dose of 60–66 Gy in 3 fractions was associated with excessive toxicity and treatment-related death. However, severe toxicity has not been noted when a "risk-adapted" dosing strategies were used [48, 49]. Studies have also shown the safety of SBRT in elderly patients. SBRT also appears to be well-tolerated in patients with severe COPD, with grade 3–4 toxicities occurring in <10% of patients [50].

There is also an ongoing debate about the role of SBRT in medically fit and operable patients. Two ambitious randomized trials, set to address this debate, closed prematurely due to slow accrual. A pooled analysis of both these two trials in operable patients showed a 16% higher 3-year survival with SBRT compared to surgery, due to a higher rate of perioperative mortality in the surgical group [51]. A propensity score matched analysis showed that rates of treatment-associated mortality and severe toxicity were lower with SBRT compared with VATS lobectomy [52]. Data from many other retrospective and prospective phase II studies of SBRT compared to surgery have shown equivocal survival outcomes. The importance of shared decision-making between oncologists and patients cannot be overemphasized in arriving at an optimal management plan based on a patient's preferences and values. The role of SBRT in operable patients continues to be studied in many ongoing studies (VALOR study, SABRTooth and STABLE-MATES).

7.2 Locally Advanced, Non-metastatic NSCLC

RT is the cornerstone in the definitive treatment of unresectable, locally advanced, non-metastatic NSCLC either alone or given concurrently or sequentially with systemic therapy. The seminal study by Perez et al. in 1980 compared different fractionation RT schedules and established the standard radiation dose of 60 Gy in 30 fractions in NSCLC [53]. Subsequent studies have tried to escalate to higher dose to target and utilized altered fractionation to improve the therapeutic ratio [54]. Although few of them did demonstrate improved local control and survival, there has also been a concomitant increase in treatment-related toxicity.

Combined modality treatment with chemotherapy was explored earliest in the CALGB 8433 trial and RTOG 8808 trial, both of which compared sequential chemotherapy followed by RT and RT alone [55, 56]. Two-year survival rates were significantly better with combined treatment in both the trials. A meta-analysis of 22 trials demonstrated significant overall benefit with chemotherapy, resulting in an absolute benefit of 3% at 2 years and 2% at 5 years [57]. Comparison between concurrent and sequential chemotherapy with radiation has shown significant benefit of concurrent schedule on overall survival (HR, 0.84; 95% CI, 0.74 to 0.95; $p = 0.004$), with an absolute benefit of 5.7% at 3 years and 4.5% at 5 years [58]. Addition of chemotherapy to hyper-fractionated RT has shown similar survival improvement but at the cost of additional grade 3 haematological and non-haematological toxicity [59].

In the CALGB 39081 phase 3 study, patients received definitive chemoradiation following induction chemotherapy versus immediate concurrent chemoradiation therapy alone for LA NSCLC [60]. This study showed that induction chemotherapy was associated with increased toxicity, but no observable survival advantage, reduction in distant metastasis or decrease in locoregional progression. Currently, there is no randomized data specifically supporting the role for consolidation chemotherapy after chemoradiation therapy for the improvement of overall survival; however, this treatment is still routinely given to address micro-metastatic disease particularly, especially if full systemic chemotherapy doses were not delivered during radiation therapy [61]. Use of targeted therapy (TKI and monoclonal antibody) concurrently with radiation has not been proven beneficial till date. Earlier studies showed increased incidence of radiation pneumonitis when erlotinib was utilized with RT [62, 63].

The advent of modern radiation techniques has prompted widespread use of three-dimensional conformal RT (3DCRT), IMRT and IGRT in treatment of NSCLC. Earlier studies established the dosimetric advantage of IMRT over 3DCRT in terms of significant reduction in doses to lung, heart and oesophagus. Many clinical studies have also shown very low incidence of grade 3 or more esophagitis and pneumonitis with IMRT [64]. However, attempts to escalate total dose in modern era have yielded mixed clinical results and need to be further studied [65].

Next generation treatment planning currently being clinically investigated in the treatment of NSCLC includes use of proton therapy, heavy ion therapy, 4π treatment planning systems and combination of RT with novel immunotherapy agents.

7.3 Postoperative RT (PORT)

PORT Meta-analysis Trialists Group collated data from 9 trials and reported a detrimental effect of PORT in patients with stage I/II and N0/1 disease [40, 66]. Many of the studies trials used older conventional RT techniques, and this might have masked a true benefit of PORT. Positive margins and gross residual disease are indications for PORT; the role of PORT in patients with completely resected N2 disease remains debatable. Some recent retrospective studies have suggested a survival benefit with PORT for pN2 disease [41]. With the use of PET-CT scans and endoscopic staging, preoperative mediastinal lymph node staging has improved vastly in the past decade, and incidentally detected pN2 disease has become a less common scenario. Recently, the LungArt trial and PORT-C trial have demonstrated no survival benefit with the addition of PORT in pN2 disease.

7.4 Palliative RT

A majority of patients with NSCLC are diagnosed with locally advanced (stage III) or metastatic (stage IV) disease who receive palliative intent radiation therapy, where the primary goal is to improve quality of life by reducing pain and other symptoms. Palliative radiation therapy can alleviate many symptoms of lung cancer including pain, cough, dyspnoea and haemoptysis. It has also been shown to improve overall quality of life in symptomatic patients [67]. In patients with stage III NSCLC unsuitable for curative therapy but who have a good performance status are candidates for systemic therapy and have a life expectancy of 3 months or more, administration of a platinum containing chemotherapy doublet concurrently with moderately hypo-fractionated palliative thoracic radiation therapy has been recommended over treatment with either modality alone.

8 Medical Management

Few of the important landmark studies pertaining to systemic therapy in NSCLC are listed in Table 2.

8.1 Early Stage

Adjuvant systemic therapy has a vital role in patients who undergo surgical resection for stage I lung cancer, especially in a subset of patients with stage IB disease who are at high risk for disease recurrence. These high-risk features include primary tumour size >4 cm, poorly differentiated histology, lympho-vascular invasion or inadequate/unknown lymph node sampling. Additionally, adjuvant systemic chemotherapy is indicated in all completely resected NSCLC patients with any node positive (N1 or more). The most commonly used adjuvant chemotherapy regimens are cisplatinum in combination with vinorelbine or etoposide. Many large multicentre randomized controlled trials and meta-analyses have shown that cisplatin-based adjuvant chemotherapy in completely resected NSCLC is associated with a significant survival advantage [34, 35, 68].

8.2 Locally Advanced

Neoadjuvant chemotherapy (NACT) followed by surgery is an option in resectable NSCLC patients with bulky or multistation mediastinal nodes. Data from 15 randomized studies showed that NACT significantly improved R0 resection rates, overall survival, time to distant recurrence, and recurrence-free survival in resectable NSCLC [69]. A phase III study comparing pre-versus postoperative chemotherapy found no difference in survival, but a larger proportion of patients completed treatment in the NACT arm [70]. However, adjuvant chemotherapy allows for more reliable pathological staging to establish if subsequent chemotherapy is appropriate.

Evidence from a meta-analysis and 12 randomized controlled trials have shown survival benefit with cisplatin-based chemotherapy and radical radiotherapy compared to radiotherapy alone [71, 72]. Data from 7 randomized trials showed that concomitant chemoradiotherapy improved survival compared with sequential chemoradiotherapy, albeit at the cost of additional toxicity, especially esophagitis [58].

8.3 Metastatic NSCLC

In the past few decades, several randomized clinical trials have investigated the effect of systemic chemotherapy in patients with metastatic NSCLC. An individual patient data meta-analysis showed that cisplatin-based chemotherapy is associated with an absolute increase in one-year survival of 5–10% in patients with metastatic disease and increased median overall survival [73]. Few other meta-analyses on published literaturea have also showed that systemic chemotherapy prolongs survival compared with best supportive care alone [57, 74].

Although platinum-based regimens have significantly higher hematologic toxicity, nephrotoxicity, and nausea and vomiting, they are considered the standard first-line treatment in advanced NSCLC. A phase III trial showed superior overall survival for cisplatin and pemetrexed combination compared to cisplatin and gemcitabine in

Table 2 Key systemic therapy studies in NSCLC

Study	Arms	OS in Months (HR)	PFS in months (HR)
Initial therapy			
Chemotherapy			
Non-squamous—multiple RCT	Platinum doublet—gemcitabine/paclitaxe/ pemetrexed	12 months—40%	4
Squamous—Multiple RCT	Doublet—paclitaxel/docetaxel/gemcitabine	12 months—35%	4
Immunotherapy			
Keynote 024 (PD L1 > 50%)	Pembrolizumab v/s chemotherapy	6 months (80.2 v/s 72.4) (0.60)	10.3 v/s 6 (0.50)
Keynote 189(PD-L1 unselected)	Pemetrexed+ platinum + pembrolizumab v/s Pemetrexed+ platinum + placebo	12 months—69% v/s 49%	8.8 v/s 4.9 (0.52)
Keynote 407 (squamous histology) (PD-L1 unselected)	Pembrolizumab or placebo and carboplatin + paclitaxel or nabpaclitaxel	15.9 v/s 11.3 (0.64)	6.4 v/s 4.8 (0.56)
IM power 131(squamous) (PD-L1 selected)	Atezolizumab +carboplatin + paclitaxel (ACP) v/s ACP	23.6 v/s 14.1 (0.56)	6.3 v/s 5.6 (0.7)
IM power 150 (non-squamous)	Atezolizumab + bevacizumab +carboplatin + paclitaxel (ABCP) v/s BCP	19.2 v/s 147 (0.62)	8.3 v/s 6.8 (0.62)
Bevacizumab			
Soria JC et al. meta-analysis	Bevacizumab + chemotherapy v/s chemotherapy	Increased OS (0.9)	Increased PFS (0.72)
Maintenance therapy—after initial chemotherapy			
Paramount	Pemetrexed v/s placebo	13.9 v/s 11 (0.76)	4.1 v/s 2.8 (0.62)
SATURN	Erlotinib v/s placebo	2.8 v/s 2.6 (0.71)	12 v/s11(0.81)
AVAPERL	Bevacizumab v/s bevacizumab + pmetrexed	–	3.7 v/s 7.4 (0.48)
Second-line			
TAX 320	Docetaxel v/s vinorelbine or ifosfamide	12 months 32% v/s 19%	Increased PFS at 26 weeks ($p = 0.005$)
Checkmate 057 (non-squamous)	Nivolumab v/s docetaxel	12.2 v/s 9.4 (0.73)	12 months (19% v/s 8%)
Checkmate 017(squamous)	Nivolumab v/s docetaxel	9.2 v/s 6 (0.59)	3.5 v/s 2.8 (0.62)
OAK	Atezolizumab v/s docetaxel	13.8 v/s 9.6 (0.73)	2.8v/s 4 (0.95) (CI-0.82-1.1)
REVEL	Ramucirumab + docetaxel v/s docetaxel	10.5 v/s 9.1 (0.86)	4.5 v/s 3 (0.76)
Stage III post CTRT			
PACIFIC	Durvalumab v/s placebo	24 months (66.3 v/s 55.6) (0.68)	17.2 v/s 5.6 (0.51)
EGFR driver mutation			
OPTIMAL	Erlotinib v/s chemotherapy	22.8 v/s 27.2 (1.04)	13.1 v/s 4.6 (0.16)
EURTAC	Erlotinib v/s chemotherapy	–	9.7 v/s 5.2 (0.37)
Mok TS et al	Gefitinib v/s carboplatin—paclitaxel	–	Subgroup analysis HR-0.78
Lux lung 3	Afatinib v/s chemotherapy	25.8 v/s 24.5 (0.91)	11.1v/s 6.9 (0.58)
AURA-3	Osimertinib 80 mg OD v/s chemotherapy	–	10.1 v/s 4.5 (0.31)
FLAURA (untreated patients)	Osmertinib 80 mg OD v/s gefitinib or erlotinib	–	18.9 /s 10.2 (0.46)
NEJ009 study	Gefitinib 250 mg or Gefitnib 250 mg + carboplatin AUC 5 + Pemetrexed 500 mg /m^2	52.2 v/s 38.8 (0.695)	20.9 v/s 11.2 (0.492)
ALK driver mutation			
Shaw et al	Crizotinib 250 mg BD v/s chemotherapy	20.3 v/s 22.8 (1.02)	7.7 v/s 3 (0.49)
Solomon BJ et al	Crizotinib 250 mg BD v/s chemotherapy	–	10.9 v/s 7 (0.45)
ASCEND-4	Ceritinib 750 mg OD v/s chemotherapy	–	16.6 v/s 8 (0.55)
ALEX	Alectinib 300 mg BD v/s Crizotinib 250 mg BD	–	Not reached v/s 10.2
ALTA	Brigatinib 180 mg OD v/s crizotinib 250 mg BD	–	12 month PFS—67% v/s 43% (0.49)

patients with adenocarcinoma and large-cell carcinoma histology; in squamous cell histology, cisplatin and gemcitabine combination, was associated with improvement in survival [75]. Hence, in patients with non-squamous histology, pemetrexed and platinum-based combination is preferred.

8.3.1 Targeted Therapy

Recent advances in our understanding of the molecular biology of NSCLC, including both the genomic alterations that drive malignancy and the mechanisms of tumour immunologic escape, have led to new and exciting treatment approaches. The identification of tyrosine kinases oncogenic activation in NSCLC, such as epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) gene rearrangement has enabled novel targeted molecular treatments.

Small molecule tyrosine kinase inhibitors (TKIs) targeting mutant EGFR have been approved by the Food and Drug Administration (FDA) as first-line agents in the treatment of mutation positive advanced NSCLC patients. Gefitinib and erlotinib are reversible competitive inhibitors of ATP for the tyrosine kinase domain of EGFR resulting in blockade of downstream pathways; they were the first EGFR TKIs to be developed. Afatinib inhibits the entire ErbB/HER family of receptors. The landmark IPASS study randomised 1217 east Asian patients with untreated stage IIIB or IV adenocarcinoma to gefitinib or chemotherapy. Patients with sensitizing EGFR mutations who received gefitinib had increased PFS (24.9% vs. 6.7%), better response rates and improved quality of life [76]. Various trials comparing different TKIs to chemotherapy, specifically in EGFR-mutated NSCLC, have consistently demonstrated that first-line EGFR TKIs resulted in superior overall response rate (ORR), PFS and quality of life compared to systemic chemotherapy. However, at present there are no published head-to-head studies comparing the efficacy of various first-line EGFR TKIs [77].

In general, most of these agents demonstrate similar efficacy, hence the choice of agent depends on toxicity or clinician preference. A study (CALGB 30406) comparing erlotinib with or without chemotherapy showed that erlotinib alone was associated with similar efficacy and fewer side effects [78]. Most patients with sensitizing EGFR mutation develop resistance and progress after 10–13 months of TKIs. EGFR T790M is associated with acquired resistance to first-line TKIs and reported in 60% patients with progression after response to initial TKIs. Osimertinib is an oral TKI that inhibits both EGFR mutations and T790M has been recently approved as a first-line therapy based on the phase I (AURA) and phase III (FLAURA) studies [79, 80].

Crizotinib is a small molecule inhibitor of the ALK, MET and ROS tyrosine kinases. Based on the results from the single-arm, global Phase II PROFILE 1005 study, crizotinib received an accelerated approval from the US FDA in 2011, because of its efficacy in ALK positive NSCLC [81]. Subsequently phase III studies have shown higher response rates and PFS benefit for crizotinib as second-line therapy in ALK positive NSCLC [82]. The PROFILE 1014 trial showed a PFS improvement of crizotinib (10.9 months vs. 7 months) over standard chemotherapy in first-line setting and has cemented its status as the first-line option in ALK positive NSCLC [83].

As with EGFR TKIs, various mechanisms (including ALK amplification, EGFR/HER1, HER2 and HER3 up-regulation, cKIT amplification and ALK mutations including L1196M) can lead to development of resistance to crizotinib for ALK rearranged NSCLC. In ALK positive patients who progress on first-line crizotinib, subsequent therapy options include alectinib, ceritinib, or brigatinib. Two phase III studies have demonstrated superiority of alectinib as first line in ALK positive NSCLC [84, 85]. Ceritinib, a second-generation ALK inhibitor, is 20 times more potent ALK inhibitor than crizotinib.

As there is a 50% sequence homology between ROS1 and ALK, ALK inhibitors such as crizotinib and ceritinib can inhibit both kinases yielding response rates of approximately 70–80%.

8.3.2 Immunotherapy

Immunotherapy for advanced NSCLC has completely changed the treatment landscape and has resulted in a new paradigm of treatment options resulting in improved survival, better response rates and safer yet unique toxicity profile compared to conventional systemic chemotherapy. Immunotherapy uses highly selective humanized monoclonal antibodies against checkpoint signals such as programmed cell death receptor (PD-1) and programmed cell death ligand (PD-L1). Blockage of these receptors and signals reactivates the immune system to target the tumour. PD-1 inhibitors such as nivolumab and pembrolizumab, and PD-L1 inhibitor, atezolizumab, are currently approved by various regulatory authorities for the treatment of advanced NSCLC.

Nivolumab, a fully human IgG4 monoclonal antibody, selectively inhibits PD-1 activity by binding to the PD-1 receptor and blocks binding to its ligands PD-L1 and PD-L2. CheckMate 057 and CheckMate 017, two recently published phase III randomized studies demonstrated the clinical benefit with nivolumab as a second-line agent for advanced squamous and non-squamous NSCLC while reducing high-grade adverse effects. Compared to chemotherapy, nivolumab had a higher OS, PFS and response duration with any PD-L1 expression levels (>1%, 5% and 10%) [86]. Pembrolizumab, another PD-1 blocker is the first immune checkpoint blockade drug to be approved as first-line treatment for metastatic NSCLC with expression of PD-L1 on at least 50% based on the KEYNOTE 010 trial [87] and KEYNOTE 024 trial [88]. PD-L1 inhibitors inhibit the interaction between PD-1 and PD-L1, thus preventing the death of tumour-specific T-cells. Atezolizumab and durvalumab are the most common drugs in this class. Currently, many ongoing studies are investigating the combination of chemotherapy/radiotherapy and immune checkpoint inhibitors in patients with NSCLC. A comprehensive review is beyond the scope of this text and can be found elsewhere [89, 90].

9 Stage-Wise Management Algorithms

See Figs. 1, 2, 3 and 4.

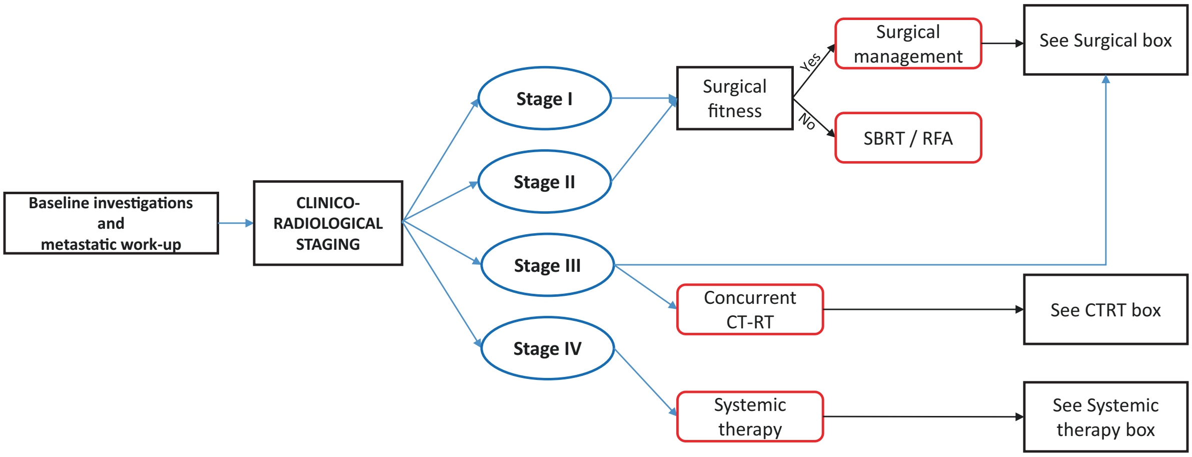
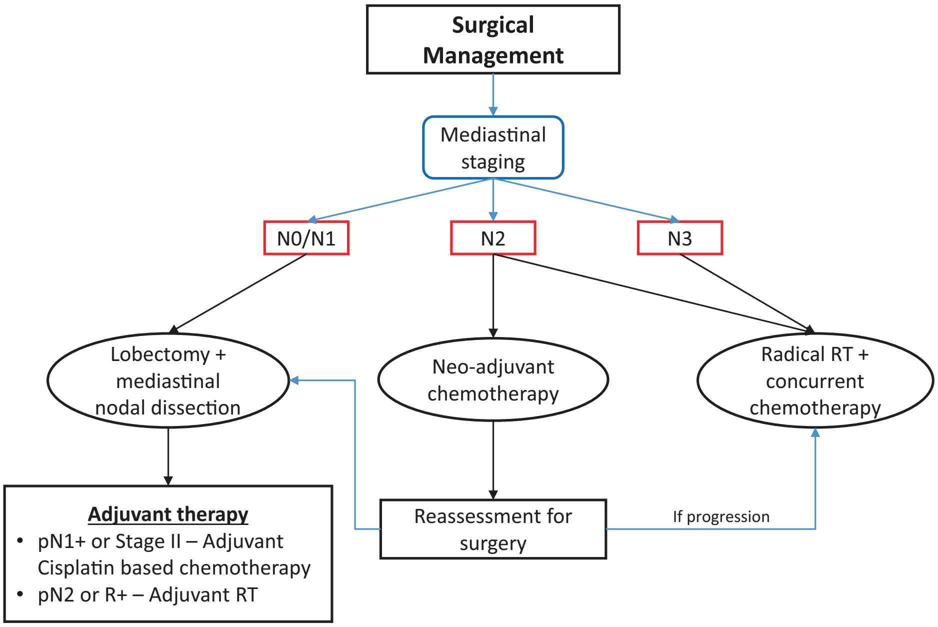

Baseline investigations and metastatic work-up
CLINICO-RADIOLOGICAL STAGING
Stage I
Stage II
Stage III
Stage IV
Surgical fitness
Yes
No
Surgical management
SBRT / RFA
See Surgical box
Concurrent CT-RT
See CTRT box
Systemic therapy
See Systemic therapy box

Fig. 1 Overview of NSCLC management

Fig. 2 Surgical management pathway in NSCLC


Surgical Management
Mediastinal staging
N0/N1
N2
N3
Lobectomy + mediastinal nodal dissection
Neo-adjuvant chemotherapy
Radical RT + concurrent chemotherapy
Adjuvant therapy
• pN1+ or Stage II – Adjuvant Cisplatin based chemotherapy
• pN2 or R+ – Adjuvant RT
Reassessment for surgery
If progression

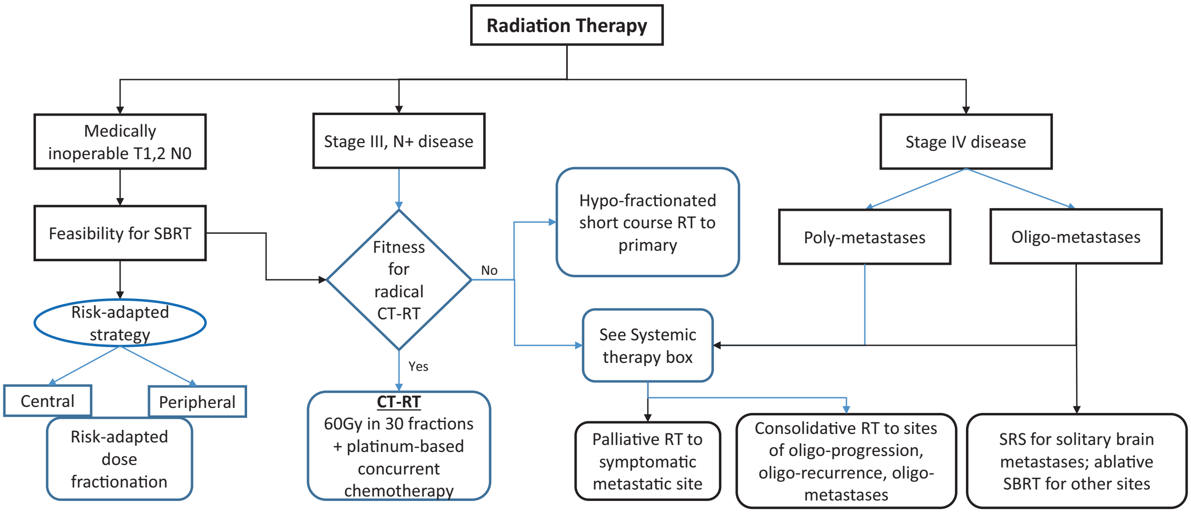

Radiation Therapy
Medically inoperable T1,2 N0
Feasibility for SBRT
Risk-adapted strategy
Central
Peripheral
Risk-adapted dose fractionation
Stage III, N+ disease
Fitness for radical CT-RT
No
Yes
CT-RT
60Gy in 30 fractions + platinum-based concurrent chemotherapy
Hypo-fractionated short course RT to primary
See Systemic therapy box
Stage IV disease
Poly-metastases
Oligo-metastases
Palliative RT to symptomatic metastatic site
Consolidative RT to sites of oligo-progression, oligo-recurrence, oligo-metastases
SRS for solitary brain metastases; ablative SBRT for other sites

Fig. 3 Radiation therapy pathway in NSCLC

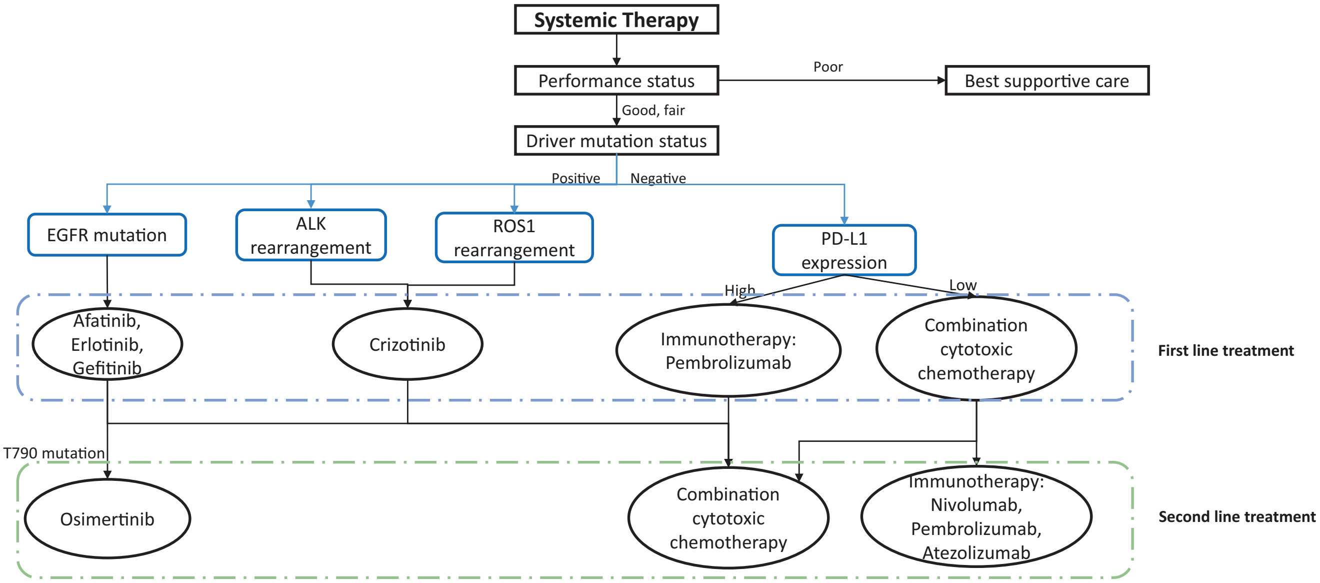

Systemic Therapy
Performance status
Poor
Best supportive care
Good, fair
Driver mutation status
Positive
Negative
EGFR mutation
ALK rearrangement
ROS1 rearrangement
PD-L1 expression
High
Low
Afatinib, Erlotinib, Gefitinib
Crizotinib
Immunotherapy: Pembrolizumab
Combination cytotoxic chemotherapy
First line treatment
T790 mutation
Osimertinib
Combination cytotoxic chemotherapy
Immunotherapy: Nivolumab, Pembrolizumab, Atezolizumab
Second line treatment

Fig. 4 Systemic therapy pathway in NSCLC

Table 3 Common toxicities in treatment of NSCLC

Treament modality	Major toxicities
Surgery	**Intra-operative complications** Injury to major vessels Cardiac arrhythmia Myocardial ischaemia Contralateral pneumothorax Other complication (usually detected late) Injury to intrathoracic nerves, oesophagus, thoracic duct **Postoperative complications** Postoperative haemorrhage Cardiac arrhythmias Right to left shunting Pulmonary complications Air leak Chylothorax Lobar torsion
Radiation therapy	Pneumonitis (acute and chronic) Oesophagitis (acute) Cardiac toxicity (chronic) Brachial plexopathy (chronic)
Systemic therapy	**Cytotoxic chemotherapy** Hematological toxicity Non-hematological toxicity (Oto-, nephro-, neuro-, hepato-, cardiac and pulmonary toxicities) **Targeted agents** Skin and GI toxicity Pneumonitis Cardiac toxicity **Immunotherapy** Dermatological toxicity, Colitis Hepatotoxicity, pulmonary toxicity, Endocrinopathies

10 Toxicity of Treatment

A few of the common toxicities encountered with various treatment modalities in NSCLC are listed in Table 3**.**

11 Stage-Wise Prognosis with Current RX

The 5-year survival rate for different stages of NSCLC is as follows, for stage IA1, IA2 and IB 92%, 83%, and 68%, IIA and IIB is 60% and 53%, stage IIIA and IIIB is 36% and 26%, stage IV is less than 10%. Over the last decade, survival in lung cancer has increased from a median overall survival of 11 months to an overall 5-year survival rate of 17.8%. Identification of EGFR and ALK mutations in stage IV NSCLC has ushered in a new era in management and portends better prognosis, with observed median overall survival of more than 30 and 40 months, respectively.

12 How We Do It at TMC

See Table 4.

Table 4 How we do it at TMC

Surgery	
SBRT Dose: 60 Gy in 3–5# for peripheral tumours; 60Gy in 8# for central tumours using conformal radiotherapy techniques. BED more than 100Gy is recommended **Definitive RT—Conventional fractionation** Dose: 60–66 Gy/30–33#/6–7 weeks with 6 MV photons using conformal radiotherapy techniques **Adjuvant PORT** Dose: 50–54 Gy/25–27#/5–6 weeks with 6 MV photons using conformal radiotherapy techniques Lung dose: (volume both lungs and subtract PTV) for DVH calculation, to keep risk of grade 2+ radiation pneumonitis less than 20%. Aim: Mean lung dose <20 Gy,V20Gy < 30–35% (concurrent chemoradiotherapy / radiotherapy)	
Palliative radiotherapy doses for locally advanced /metastatic lung cancer **Thoracic palliative radiotherapy / superior vena cava syndrome:** 30–39 Gy/10–13#/2.5 weeks or 20 Gy/5# over 1 week 17 Gy/2 Fr/weekly once (for poor performance status patients) **Metastatic disease** Parenchymal brain metastases with good performance status: Whole brain radiotherapy: 30 Gy/10#/2 weeks followed by boost to gross lesion With poor performance status: Whole brain radiotherapy—20Gy/5#/1 week Spinal cord compression: 30 Gy/10#/2 weeks (or) 20Gy/5#/1 week (or) 16Gy/2#/1 week Painful bone metastases: 6–8 Gy/1#; 20Gy/5#/1 week in case of associated pathological Fracture or soft tissue mass Rarely, hemi-body irradiation may be used for disseminated bone metastases **Endobronchial radiotherapy** Salvage treatment for recurrent/residual endobronchial lesion 7.5 Gy per # for 2 sittings a week apart	
Systemic therapy—NSCLC metastatic	
Front line—No targetable mutation **Non-squamous**	Paclitaxel 200 mg/m^2 + carboplatin AUC 6 + Atezolizumab 1200 mg + Bevacizumab 15 mg/kg (regardless of PDL 1) q 21 days Pembrolizumab 200 mg agent if PD L1 > 50%q 21 days Pemetrexed 500 mg / m2 + carboplatin AUC -6 + Pembrolizumab 200 mg if PD L1 < 50% q 21 days Paclitaxel 200 mg/m^2 + carboplatin AUC 6+ bevacizumab 15 mg/kg Pemetrexed 500 mg/m^2 + carboplatin AUC—6 q 21 days
Front line—No targetable mutation **Squamous**	Nab pacliataxel 100 mg/m^2 + carboplatin AUC—6 + pembrolizumab 200 mg q 21 days Gemcitabine 1200 mg/m^2 + Carboplatin AUC—6 q 21 days
Targetable mutations	
EGFR mutations	1. Afatinib 2. Erlotinib 3. Gefitinib 4. Osimertinib(T790M positive) 5. Erlotinib + bevacizumab
ALK gene rearrangements	1. Crizotinib 2. Ceritinib 3. Alectinib
Ros mutation	1. Crizotinib 2. Ceritinib
High-level met amplifications	1. Crizotinib

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Small Cell Lung Cancer

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Abbreviations

3D-CRT	Three-dimensional conformal radiation therapy
4DCT	Four-dimensional computed tomography
CAV	Cyclophosphamide Adriamycin and vincristine
CBC	Complete blood count
EP	Etoposide
IASLC	International Association for the Study of Lung Cancer
IMRT	Intensity-modulated radiation therapy
MIP	Maximum intensity projection
OS	Overall survival
PCI	Prophylactic cranial irradiation
SCLC	Small cell lung cancer
SIADH	Syndrome of inappropriate antidiuretic hormone
VALSG	Veterans' administration lung study group

1 Introduction

Lung cancer is primarily classified histologically into non-small cell and small cell lung cancer. Small cell lung cancer (SCLC) is a neuroendocrine tumor with a high malignant potential. It is a highly aggressive tumor with a rapid doubling time and high growth fraction. SCLC has a high propensity for nodal metastasis, and nearly two-thirds present with metastatic disease with visceral and skeletal metastases. SCLC is a very chemo- and radiosensitive tumor, and both treatments form the mainstay of treatment.

2 Incidence and Epidemiology

Lung cancer is one of the most common cancer worldwide and fourth most common in India. It is also a leading cause of cancer-related mortality in the world and ranked third most common cause in India [1]. It accounts for approximately 10% of overall cancer mortality in India. SCLC accounts for 10–15% of all lung cancer cases worldwide. Smoking is the commonest risk factor for SCLC contributing to 95% of cases worldwide, and it mirrors the incidence of smoking patterns. SCLC is more prevalent in males as compared to females owing to more smoking rates; however, this difference is now shrinking and prevalence rates are same [2].

SCLC can present with symptoms due to local extension, extrathoracic extension, constitutional or paraneoplastic disorders. SCLC usually presents as a central lung mass with involvement of hilum as compared to peripheral disease in non-small cell lung cancer. Local symptoms like cough, chest pain, hemoptysis, and dyspnea are the most common symptoms at presentation. SCLC can also present with dysphagia, hoarseness, and superior vena cava syndrome owing to the compression or invasion of the esophagus, recurrent laryngeal nerve, and great vessels, respectively. Superior vena cava syndrome is present in 10% of patients and present with puffiness of the face, engorged neck veins, and breathing difficulty. Patients often report anorexia, fatigue, and weight loss due to the systemic nature of the disease. The majority of SCLC patients have metastatic disease at diagnosis [2] and have associated symptoms. Bony involvement is usually osteolytic and presents with bone pain. It can also manifest with metastatic spinal cord compression. Hepatic involvement is generally asymptomatic with increase in bilirubin, transaminase, and alkaline phosphatase. Adrenal lesions are asymptomatic and detected on imaging. CNS involvement is symptomatic and presents with a headache, vomiting, seizure, and associated symptoms depending upon the location of the lesions.

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SCLC is the commonest cause of paraneoplastic syndrome among solid tumors [3] and can present with symptoms related to hormone secretion or immune-mediated response. The most common paraneoplastic syndrome is syndrome of inappropriate antidiuretic hormone (SIADH), which can cause euvolemic hyponatremia, concentrated urine, and reduced plasma osmolality. Cushing disease (excess ACTH secretion), Lambert-Eaton syndrome, hypercalcemia, and hypertrophic pulmonary osteoarthropathy are the other common paraneoplastic disorders seen in SCLC.

3 Evaluation and Work-Up

Complete history and detailed physical examination of a patient suspected to have SCLC is of foremost importance as the patient can present with varied manifestation as described above. Chest X-ray is usually the first investigation and can demonstrate mediastinal widening, atelectasis, and pleural effusion. Blood investigations typically include complete blood counts (CBC), serum electrolytes, kidney and liver function tests, serum calcium, and lactate dehydrogenase. Imaging plays a very important role in the staging of SCLC. Contrast-enhanced computed tomography (CT) of the chest and upper abdomen can demonstrate the extent of the primary disease, mediastinal adenopathy, and adrenal gland involvement. Bone metastases can also be seen on the CT. F-18, fluorodeoxyglucose positron emission tomography (F^{18} FDG PET)/CT is performed to rule out the distant metastatic disease. If FDG PET is not available, then bone scintigraphy with technetium-99m methylene diphosphonate is recommended. FDG PET-CT can upstage the disease in approximately 15–20% of patients [4] and changes treatment decisions and radiotherapy target volumes [5]. Magnetic resonance imaging (MRI) of the brain is recommended for all patients, since brain metastases can present in 10–15% at diagnosis, including 10% of asymptomatic patients [6]. Incidence of brain metastases increases with the stage of the disease. Most common sites of metastatic disease are bone, liver, brain and adrenal glands.

4 Pathology

The diagnosis of SCLC can be established by fluid cytology, percutaneous transthoracic biopsy or bronchoscopic biopsy. On H& E stain, SCLC is a small blue round cell tumor with scant cytoplasm, finely granular nuclear chromatin, absent or inconspicuous nucleoli with ill-defined borders [3, 7]. SCLC has a high mitotic rate, and extensive necrosis is typically present. Crush artifact is more commonly encountered in SCLC in biopsy specimens. In resected specimens, small cell is usually larger than seen in biopsy specimens because of better fixation. SCLC is usually described as pure SCLC or combined SCLC. Combined SCLC is usually present in combination with another non-small cell histologies adenocarcinoma, squamous and large cell carcinoma. In difficult diagnosis, immunohistochemistry markers can be useful like pan-cytokeratin antibody (AE1/AE3), neuroendocrine markers (chromogranin, synaptophysin, CD56), thyroid transcription factor (TTF-1), and ki-67. TTF-1 is positive in approximately 75–80% of cases [8, 9]. Ki-67 is a proliferative marker and ranges up to 60–80% in SCLC and can be used to differentiate other neuroendocrine tumors from SCLC.

5 Staging

Historically, SCLC for all practical purpose was stage into limited stage (LS) and extensive stage (ES) in 1950s by the Veterans' Administration Lung Study Group (VALSG) depending on whether the disease can be encompassed in a single and safe radiation portal [10, 11]. Limited stage was defined as disease confined to one hemithorax, local extension, and ipsilateral supraclavicular node included if they can be encompassed in safe radiation portal. All other disease that cannot be encompassed in a radiation portal including extrathoracic metastases were defined as extensive stage. In 1989, the International Association for the Study of Lung Cancer (IASLC) modified limited stage definition as disease confined to one hemithorax with regional lymph node metastases including hilar, ipsilateral, or contralateral mediastinal/supraclavicular nodes. They also included ipsilateral pleural effusion irrespective of cytology in limited stage. This staging system was used in clinical practice for almost six decades. As majority present in advance or metastatic stage surgery has no role, hence, TNM staging was very infrequently used in clinical practice. However, it was applicable for SCLC and few surgical series showed TNM to be of prognostic significance. In year 2007 with proposed changes for seventh edition of TNM, IASLC recommended that AJCC TNM should be used for staging of SCLC [12]. For TNM staging and grouping, kindly refer to the chapter of NSCLC. Though prognostically validated, this staging system is too cumbersome, and management remains same for most of the stages in routine clinical practice. Disease more extensive than described above is considered extensive stage (ES) disease. Accurate staging of SCLC is essential since treatment decision changes accordingly.

6 Principles of Management

As SCLC is a very aggressive malignancy, the principle is to start treatment as early as possible after confirmation of diagnosis and discussion in multidisciplinary tumor board.

Table 1 Management of SCLC

6.11.Stage	Standard management	Radiation	Chemotherapy	5-year OS
Limited stage (T1, T2), N0, M0	Mediastinal lymph node dissection and lobectomy	If node positive	Adjuvant chemotherapy cisplatin + etoposide	40–45%
Limited stage (T1-T4, N1-N3, M0)	Concurrent CTRT	Conformal RT (dose—45 Gy/30 Fr, 1.5 Gy bid) or 60 Gy in 30 Fr	Cisplatin + etoposide (3 weekly)	20–25%
Extensive stage (any T, any N, M1)	Palliative chemotherapy	Any response—PCI (dose-25 Gy/10 Fr) ± consolidative RT to the chest	4–6 cycles of carboplatin + etoposide (3 weekly)	0–5%

OS overall survival, *CTRT* chemoradiation, *RT* radiotherapy, *PCI* prophylactic cranial irradiation, *T* tumor, *N* node, *M* metastases

Overall management of SCLC is outlined in Table 1. Majority presents with metastases (extensive stage) hence, chemotherapy is the mainstay of treatment of SCLC. Symptomatic treatment and supportive care are also indicated apart from chemotherapy. In LS-SCLC, a combination of chemotherapy and radiation therapy is the standard of care. Prophylactic cranial irradiation is recommended after completion of therapy in LS and ES-SCLC to reduce the incidence of brain metastases. Surgery is done in less than 5% of LS-SCLC. Overall, SCLC has a dismal survival rate with a median OS of 3–4 months in the absence of treatment. According to SEER database, 5-year OS for limited stage is 20–25% and < 5% for extensive stage disease. TNM staging better prognosticates patients of SCLC and 5-year OS of stage I, II, III, and IV is reported as 38%, 18%, 11%, and 1%, respectively.

7 Limited Stage SCLC

7.1 Surgical Management

Surgery has a very limited role to play in the management of localized SCLC. In very early stage with no documented mediastinal nodes on PET-CT and EBUS (T1/T2 N0 M0), surgical resection consists of mediastinal lymph node dissection with lobectomy [13]. The incidence of lymph node metastases is still considerably high and hence adjuvant chemotherapy is recommended for all patients after resection. The adjuvant chemotherapy consists of four cycles of cisplatin-based regimens [14]. Pathological node-positive patients will require adjuvant concurrent chemoradiation therapy [15]. In ES-SCLC, surgery has no role except palliative fixation of pathological fractures.

7.2 Radiation Management

In very early-stage SCLC (T1/T2N0M0) patients, those who are not suitable or refused surgery, stereotactic body radiation therapy could play a role. However, there is very limited data available as patient population in this cohort is extremely small. A recent systematic review concluded that SBRT in stage I SCLC could be a potential option with comparable outcomes and no added toxicities [16]. In majority of LS-SCLC, definitive radiation therapy concomitant with Cisplatin-Etoposide chemotherapy is the standard of care. Two meta-analysis including Pignon et al. of 13 randomized controlled trials (RCTs) showed that thoracic radiotherapy improved overall survival (OS) by 5.4% at 3-year vs. chemotherapy alone [17, 18]. As lung tumor moves with respiration, radiation planning with adequate immobilization and motion management strategies like four-dimensional computed tomography (4DCT), gating and tracking should be utilized according to the institutional protocol. At TMH, 4DCT radiation planning with target delineation on maximum intensity projection (MIP) datasets and treatment planning on free breathing scan is done. Three-dimensional conformal radiation therapy (3D-CRT)/intensity-modulated radiation therapy (IMRT) are the preferred radiation planning techniques.

7.2.1 Timing of Thoracic RT

Timing of thoracic RT with chemotherapy has always remain a topic of debate and controversy. Various phase III studies have evaluated the timing of thoracic RT with chemotherapy and showed mixed results for survival outcomes. Three RCT showed significant benefit in terms of OS for early thoracic RT compared with delayed thoracic RT [19–21]. Several systematic review and meta-analysis also reported that early concurrent thoracic RT is beneficial as compared to delayed RT [22–24]. Individual patient data meta-analysis also supports early and shorter thoracic RT for overall survival benefit as compared to delayed and longer RT [25]. Also, overall treatment duration from the start of chemotherapy to last day of radiation also predicted outcome in one of the systematic reviews [23]. NCCN guidelines also recommend that concurrent thoracic RT should commence from cycle one or two of chemotherapy.

7.2.2 Dose of Thoracic RT

Various total doses and fractionation schedules of radiation therapy are supported in literature (Table 2), and different institutes use dose schedules according to their institutional

Table 2 Studies evaluating accelerated regimens of RT in LS- SCLC

Study	RT	CT	OS	PFS	Esophagitis (%)
INT 0096 (1999)	B.I.D (45 Gy/30 Fr) OD (60 Gy/30 Fr)	EP	26% (5 years) 16% (5 years)	29% (2 years) 24% (2 years)	27 11
Schild et al (2004)	BID—48 Gy/32 Fr OD—50.4 Gy/28 Fr	NACT −3 #EP ➔ CTRT	21% (5 years) 22% (5 years)	21% (5 years) 19.8% (5 years)	05 12
RTOG 0239 (2012)	61.2 Gy/ 34 Fr [1.8 Gy OD (d1–d22) ➔1.8 Gy B.I.D (d22–d33)]	EP	36.6% (2 years)	19.7% (2 years)	18
CONVERT (2017)	BID—45 Gy/30 Fr OD—66 Gy/33 Fr	EP	56% (2 years) 51% (2 years)	15.4 months 14.3 months (median)	19 19

OD once daily, *BID* twice daily, *Fr* fraction, *RT* radiotherapy, *CT* chemotherapy, *EP* etoposide cisplatin, *PFS* progression-free survival, *OS* overall survival

practice. Radiation doses schedule ranges from accelerated regimen of 45 Gy/30 fraction at 1.5 Gy/fraction twice daily, 6 h apart over a period of 3 weeks [26] to hypofractionated regimen of 40 Gy/15 fractions over 3 weeks [27] or conventional regimen of 60 to 66 Gy/30–33 fraction once daily at 2Gy per fraction over a period of 6 weeks. Accelerated fractionation regimens are used to counter rapid proliferation of small cell tumors. EORTC study published in 1999 showed accelerated twice-daily radiation (45 Gy/30 Fr) resulted in improvement of 5-year OS of 26% vs. 16% for once daily (45 Gy/30Fr) ($P < 0.04$). The incidence of grade III esophagitis (27%) was higher in twice-daily arm. Criticism of this trial was the lower biological dose in once-daily arm compared to twice-daily arm. Phase II study by RTOG 0239 evaluated accelerated regimens of 61.2 Gy over 33 days along with cisplatin and etoposide and demonstrated inferior 2-year OS of 37% and lower grade III esophagitis of 18% compared to INT 0096 [28]. Contrary to INT 0096 study, recently published superiority trial of once daily over twice daily (CONVERT) showed no significant difference between once-daily and twice-daily regimens and concluded that twice-daily regimens should continue to be the standard dose regimens. However, in resource-constrained countries like India, once-daily regimen of 60 Gy/30 fractions is most commonly used regimen because of logistical reasons.

7.2.3 Role of PCI

After completion of planned treatment, prophylactic cranial irradiation (PCI) is recommended at a dose of 25 Gy/10 fractions since the brain is the common site of relapse. Two-year cumulative risk of developing brain metastases is approximately 50% [29]. Meta-analysis of 7 randomized trials by Auperin et al. has shown a reduction in the risk of brain metastases by 50% and improvement in overall survival by 5.4% at 3 years with PCI compared with no PCI [30]. A second meta-analysis also confirmed the beneficial effects of PCI [31]. However, the role of PCI is questioned in elderly, larger size tumors and patients with poor mentation [32]. Different dose fractionation schedules are used for PCI but most commonly used is 25 Gy/10 fraction. An RCT comparing 25 Gy versus higher dose of 36 Gy showed no difference in the incidence of brain metastases but worsened overall survival with higher dose [33]. PCI has more beneficial effect if started early after the completion of concomitant chemoradiation than delayed after the completion of chemotherapy cycles [34, 35]. Prospective literature is limited except one small RCT which shows no significant benefit of early PCI within 60 days of induction treatment although timing of chemotherapy was confounding factor [36]. PCI if delayed, then higher doses of PCI are required for reducing the incidence of brain metastases [37]. PCI has been shown to cause neurocognitive deficits (NCD) in various studies [37, 38]. Various other factors affect neurocognitive decline like total dose and fractionation, age, type, and timing of chemotherapy [39, 40]. Pre- and post-PCI neurocognitive assessment were done in a single study and showed that approximately 50% of patients had pre-existing neurocognitive deficits. Also, NCD was not sustained and showed continuous improvement with time [41]. Memantine and hippocampal avoidance are the strategies used to treat and prevent neurocognition decline with PCI [42, 43].

7.3 Chemotherapy

Chemotherapy is the main form of treatment in the management of SCLC because of its disseminated nature. In limited stage, cisplatin and etoposide (EP) regimen is the standard of choice based on the results of studies partly from both, limited and extensive SCLC (Table 3). Cisplatin is given at a dose of 80 mg/m^2 IV on day 1 and etoposide 100 mg/m^2 IV on day 1–3 every three week. Initially, Cyclophosphamide, Adriamycin and Vincristine (CAV) based regimen was used for the treatment of SCLC with good response rates. In a randomized comparison of CAV, EP or alternating regimens in 288 patients by Fukuoka et al., they showed significantly

Table 3 Chemotherapy trials in LS and ES-SCLC

Study	Arms	OS (months)		PFS/HR of survival distribution		Toxicity	
Fukoka et al	CAV	12.4	$p = 0.80$	–		Leucopenia ($p < 0.001$)	78%
	EP	11.7		–			46%
	CAV /EP	16.8		–			72%
ELCWP (meta-analysis)	I-CDDP vs. non CDDP or VP-16	–		0.70		–	
	II-VP-16 vs. non CDDP or VP-16	–		0.72		–	
	III- CDDP + VP-16 vs. non CDDP or VP-16	–		0.57		–	
	IV—CDDP + VP-16 vs. VP-16	–		0.74		–	
COCIS meta-analysis	CDDP based	9.6	HR 1.08	5.5	HR1.1	Neutropenia	86 vs. 90(0.357)
	Carboplatin based	9.4		5.3		Low platelets	39 vs. 71(0.001)
						CINV	72 vs. 63(0.12)
						Nephrotoxicity	25 vs. 10 (0.001)
ES-SCLC							
IMpower 133	VP-16+ carboplatin + Atezolizumab vs. VP-16 carboplatin + placebo	12.3 vs. 10.3 (HR-0.70)		5.2 vs. 4.3 (HR-0.77)			

CDDP cisplatin, *VP-16* toposide, *CAV* cyclophosphamide + Adriamycin + vincristine, *EP* etoposide platinum, *IP* irinotecan platinum, *CINV* chemo-induced nausea and vomiting, *PFS* progression-free survival, *OS* overall survival, *HR* hazards ratio

better response rates with EP and alternating regimens as compared to CAV regimen [44]. Two systematic review and meta-analysis also showed superiority of cisplatin and etoposide-based regimens in terms of response rates and overall survival as compared to other alkylating agents [45, 46]. However, cisplatin has higher non-hematologic toxicity rates in the form of nephrotoxicity, ototoxicity, and neurotoxicity and hence cisplatin substitutes with better toxicity profile-like carboplatin have been tested in various RCTs in initial management of SCLC. Meta-analysis with individual patient data demonstrated equivalent OS, PFS, and ORR; however, hematologic toxicity were significantly less for cisplatin-based regimens [47]. Thus, cisplatin or carboplatin plus etoposide is widely used initial regimen for LS-SCLC along with early thoracic RT.

8 Extensive Stage SCLC

Majority of patients present in extensive stage disease and have distant metastases, pleural or pericardial effusion or para neoplastic syndromes. Initial management depends upon initial presentation and directed at symptomatic relief and early initiation of systemic therapy. Patients presenting with superior vena cava syndrome can be managed with endovascular stenting which gives good immediate symptomatic relief with minimal toxicity. Chemotherapy also gives fast symptomatic relief in approximately 80% patients as SCLC is a very chemo-sensitive tumor. Radiation therapy is also recommended as initial treatment or as adjuvant to stenting. Effect usually takes 48 to 72 h and majority will give symptomatic relief within 1 week. Tumor lysis syndrome should be managed with adequate hydration, appropriate electrolyte correction, and xanthine oxidase inhibitor therapy.

8.1 Chemotherapy

Platinum-etoposide doublet chemotherapy for 4–6 cycles is the initial recommended treatment for extensive stage SCLC. As stated above in LS-SCLC, two meta-analyses have shown superiority of EP regimen over other alkylating regimens. Various RCT also evaluated irinotecan platinum versus EP regimen in untreated ES-SCLC with contradictory results. Meta-analysis by Jiang et al. showed similar PFS and suggested possible benefit in OS with different toxicity profile. Irinotecan regimens produced less hematological toxicity but higher grade 3 or 4 vomiting and diarrhea. They concluded that irinotecan-based regimen is a good alternative to EP regimen in ES-SCLC [48]. Various other chemotherapeutic agents like epirubicin, topotecan, taxanes were combined with cisplatin on the basis of phase II studies to improve the response rates; however, they failed to show any significant benefit. Other strategies like alternating non-cross resistant regimens, multiple drug combinations, and dose intensification also failed to show any benefit over EP regimen. Therefore, cisplatin and etoposide regimen remains the standard of choice for initial management of extensive stage SCLC.

8.2 Duration of Treatment

Four to 6 cycles of EP regimen is the acceptable standard duration; however, it is not well defined in literature.

8.3 Targeted/Immunotherapy

Bevacizumab-based maintenance regimens after completion of planned PE regimens have also been tested in a phase III trial and concluded no significant benefit in OS. Recently, immune checkpoint inhibitors have gained importance since its success in NSCLC and have also been tested in SCLC. In a recently published RCT, carboplatin and etoposide were given concurrently with either atezolizumab, a PD-L1 inhibitor, or placebo for 4 cycles and then as maintenance atezolizumab versus placebo till disease progression. It showed a significant increase in median OS (HR −0.70) and PFS (HR −0.77) with comparable toxicity profile [49].

8.4 Radiation Therapy

After completion of planned chemotherapy, if there is no progressive disease, PCI is recommended to reduce the incidence of brain metastases in future. EORTC published a randomized study in 2007 which showed a statistically significant reduction in the risk of brain metastases, improvement in disease-free survival, and overall survival with PCI compared to no PCI [50]. The cumulative risk of symptomatic brain metastases at 1 year reduced from 40.4% to 14.6% with PCI. Criticism of this study was that brain imaging was not done before randomization to rule out brain metastases. As PCI has neurocognitive side effects, many studies have questioned the benefits of PCI especially in elderly or patients with poor mentation status at baseline as the prognosis of ES-SCLC is extremely poor. Recently published multicentric RCT of PCI vs. no PCI from Japan [51] acquired MRI brain at baseline and at follow-up assessment. The results showed that PCI did not improve OS and DFS but reduced the risk of brain metastases. Cumulative incidence of brain metastases at 18 months in the PCI group was 40.1% as compared to 63.8% in the observation group. Hence, PCI in ES-SCLC remains controversial until this date.

Consolidative RT to the chest after completion of planned chemotherapy in ES-SCLC is also a topic of debate. Jeremic et al. in 1999 published a RCT of a subset of patients with good response with CR at distant level and at least PR at primary level between accelerated hyper fractionated RT (54Gy in 36 fractions twice daily over 18 days) with chemotherapy compared with additional CT only and demonstrated a good OS rate in favor of consolidative RT to chest [52]. Slotman et al. in 2015 published another RCT in patients with any response to CT between consolidative RT to the chest (30 Gy in 10 fractions daily) compared with observation. The primary endpoint of 1-year OS did not show any benefit of RT (33% vs. 28%, $p = 0.066$); however, 2 years OS was significantly better (13% vs. 03%, $p = 0.004$) with reduced intrathoracic progression [53]. Secondary analysis showed patients benefitted from RT if any residual disease [54] or fewer than two sites of extrathoracic metastases [55]. Meta-analysis of three RCT showed improvement in progression-free survival with HR of 0.72 with reduction in intrathoracic failure, but no benefit in OS with HR of 0.88 [56]. Aggressive RT to the chest and less than four extrathoracic metastases was also studied in a phase II RCT in comparison to PCI alone and showed no difference in OS rate at 1 year but, as expected, resulted in lower rates of progression [57].

Palliative radiation therapy to symptomatic sites such as bone or brain is often warranted during the initial management of ES-SCLC. Doses ranging from 8 Gy in single fraction to 20–30 Gy in multiple fractions predominantly depend upon performance status, site of metastases, and bulk of the disease. Palliative RT gives good symptomatic relief in bony pain, cord compression, and brain metastases related symptoms.

9 Relapsed SCLC

SCLC usually relapse in majority of patients within initial 10–12 months in limited stage and 4–6 months in extensive stage. Treatment of relapse SCLC depends on patient performance status, time to relapse, and response to initial therapy. Broadly, if relapse occurs within first 6 months, initial platinum-based chemotherapy can be repeated. Various second-line single agents or two drug combination have been tested at relapse with very little success. Single agent's chemotherapeutic drugs like topotecan, irinotecan, taxanes, gemcitabine, vinorelbine, etc. have showed success in controlling the disease. In a multicenter randomized study, topotecan was compared with CAV regimen and showed comparable response rates with very good symptom control rates. Immune checkpoint inhibitors like nivolumab and ipilimumab have been tested in various phase II studies recently; however, no phase III study data is available till date. FDA has approved nivolumab as third-line treatment option.

10 Future Perspective

Immune checkpoint inhibitors alone or in combination with standard chemotherapy are being studied in various phase II studies. Hopefully, it would change the management of SCLC and improve treatment outcomes.

Table 4 Management of SCLC at TMH

Stage	Radiation	Chemotherapy	Surgery
Limited stage	60 Gy in 30 Fr OD with 3D-CRT/IMRT technique (usually with second cycle of CT)	Cisplatin (80 mg/m^2, D1) and etoposide (100 mg/m^2, D1-D3) every 3 weeks for 4–6 cycles f/b active surveillance	Lobectomy and mediastinal LN dissection (very rarely done)
Extensive stage	PCI—24.75 Gy/11 Fr if any response after chemotherapy	Carboplatin –AUC 5-6 (preferred) + Etoposide (100 mg/m^2, D1-D3) + Atezolizumab 1200 mg/m^2 every 3 weeks for 4-6 cycles f/b Atezolizumab maintenance till progression/toxicity. Alternative—Cisplatin 75 mg/m^2 d1 or 25 mg/m^2 d1-d3 and etoposide (as above) 3 weekly for 4–6 cycles. In relapse <6 months—Topotecan 1.5 mg/m^2 IV daily over 30 min. Repeat cycle every 3 weeks. Days 1–5	Palliative fixation of pathological fractures
	SVC syndrome Good GC—20 Gy/5 Fr Poor GC—17Gy/2 Fr		
	Bone metastases 8 Gy/single fraction 20 Gy/5 Fr (soft tissue)		
	Brain metastases 20 Gy/5 Fr (most common)		

OD once daily, *Fr* fraction, *3D CRT* three-dimensional conformal radiotherapy, *IMRT* intensity-modulated radiotherapy, *AUC* area under curve, *SVC* superior vena cava, *GC* general condition

11 How We Do It at TMC (Table 4)

All patients get the initial work-up done, including CT-guided biopsy, PET-CT, and MRI brain at baseline. Appropriate investigations required for fitness of chemotherapy and radiation therapy (pulmonary function test) are usually performed. All limited stage disease (TNM stage I, II, and III) are treated with concurrent chemoradiation therapy with cisplatin and etoposide as preferred chemotherapeutic agents on 3 weekly regimens. Radiation therapy planning is done with motion encompassing techniques—4D CT to account for tumor motion. All patients are planned with conformal techniques (3D CRT/IMRT/VMAT) with image guidance to a dose of 60 Gy/30 fractions treated once daily. PCI is recommended in all patients with parallel opposed techniques to a dose of 25 Gy/10 fractions. In less than 5% of patients, surgery is recommended for node-negative early-stage SCLC patients with lobectomy and mediastinal lymph node dissection after ruling out mediastinal node involvement with EBUS and PET-CT. First follow-up is usually done at 8 to 10 weeks, and blood investigations and PET-CT are done for response assessment. Thereafter, 3-month follow-up with CT thorax done every 6 months for 2 years and then 6 monthly follow-up until 5 years.

In ES-SCLC, platinum-based palliative chemotherapy for 4–6 cycles is the recommended treatment. Response assessment is done after every 3 cycles. Appropriate palliative radiation therapy to symptomatic sites if required and early palliative care referrals are usually sought. After completion of planned chemotherapy, response assessment is done with CT imaging and if partial or complete response, PCI is usually offered.

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Mediastinal Tumors

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Abbreviations

AFP	Alpha-fetoprotein
anti-AchR	Anti-acetylcholine receptor
beta-HCG	Beta-human chorionic gonadotropin
DW MRI	Diffusion-weighted MRI
GCT	Germ cell tumors
IMRT	Intensity-modulated radiotherapy
ITMIG	International Thymic Malignancy Interest Group
IV	Intravenous
LDH	Lactate dehydrogenase
MG	Myasthenia gravis
MRI	Magnetic resonance imaging
NSGCT	Nonseminomatous germ cell tumors
PRCA	Pure red cell aplasia
TK	Tyrosine kinase
VATS	Video-assisted thoracoscopic surgery
WHO	World Health Organization

1 Introduction

Mediastinal tumors include a heterogeneous group of neoplasms, both benign and malignant arising from the mediastinum. The mediastinum is defined as a closed cavity starting superiorly from the thoracic inlet to the diaphragm inferiorly, bounded on either sides by lung hila, anteriorly by the sternum and posteriorly by the vertebrae. It is further divided into three or four compartments to help categorize tumors according to their site of origin and location. The three-compartment model describes anterior, middle and posterior divisions, while the four-compartment model has an additional superior mediastinal compartment [1]. The anterior compartment extends from the posterior surface of the sternum to the anterior aspect of the great vessels and pericardium. The thymus, lymph nodes, internal mammary arteries, connective tissue and fat are the major components. The middle compartment contains the pericardium, heart, great vessels, airway and esophagus and is bounded by the pericardium anteriorly and the ventral surface of the thoracic spine posteriorly. The posterior compartment includes the spine and the costovertebral sulci. It contains the neurovascular bundles, spinal ganglia, sympathetic chain, lymphatic tissue, descending thoracic aorta, esophagus, azygos veins and fat.

2 Incidence and Epidemiology

Thymomas, neurogenic tumors and benign cysts account for approximately 60% of mediastinal masses while lymphoma, teratomas and granulomatous diseases contribute to the rest. The majority (50%) of mediastinal tumors arise in the anterior mediastinum including thymoma, teratoma, lymphoma and thyroid disease (Table 1) [2]. Masses of the middle mediastinum are usually congenital in origin and cystic,

Table 1 Anatomical location of mediastinal mass

Anterior mediastinum	Middle mediastinum	Posterior mediastinum
Thymoma	Lymphoma	Neurogenic tumors
Teratoma, seminoma	Pericardial cyst	Bronchogenic cyst
Lymphoma	Bronchogenic cyst	Paravertebral abscess
Intrathoracic goiter		Meningocele
Carcinoma		Diaphragmatic hernia
Lipoma		
Parathyroid adenoma		

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while those arising in the posterior mediastinum are most often neurogenic tumors [3]. While exact figures regarding incidence are unknown for this heterogeneous group, the incidence of thymic neoplasms is around 1.5 per million person-years as per the SEER database.

3 Clinical Presentation

The clinical presentation of mediastinal neoplasms is variable. Most often, patients present with an incidental finding on imaging during routine clinical examination. Such incidentally discovered masses generally tend to be benign. Malignant masses are more likely to be symptomatic. Symptoms may be due to compression or infiltration of surrounding vital structures or systemic due to paraneoplastic syndromes. Cough (60%), chest pain, fever and dyspnea are the most common symptoms at presentation. Some tumors may present with more life-threatening symptoms like superior vena cava obstruction, stridor due to tracheal compression or hypotension due to cardiac or pulmonary artery compression. Involvement of nerves is a common finding, particularly in malignant tumors, with the recurrent laryngeal nerve, phrenic and the posterior nerve roots being most commonly affected. Systemic symptoms are typically due to the secretion of excess hormones, antibodies or cytokines. A variety of paraneoplastic syndromes are known to be associated with mediastinal masses (Table 2).

Table 2 Paraneoplastic syndromes associated with mediastinal masses

Syndrome	Tumor
Myasthenia gravis RBC aplasia Hypogammaglobulinemia Good syndrome Whipple's disease Megaesophagus Myocarditis	Thymoma
Multiple endocrine adenomatosis Cushing's syndrome	Carcinoid Thymoma
Hypertension	Pheochromocytoma Chemodectoma Ganglioneuroma
Diarrhea	Ganglioneuroma
Hypercalcemia	Parathyroid adenoma Lymphoma
Hypoglycemia	Mesothelioma Teratoma Fibrosarcoma Neurosarcoma
Osteoarthropathy	Neurofibroma Mesothelioma
Vertebral anomalies	Enteric cysts
Opsomyoclonus	Neuroblastoma

4 Evaluation and Work-Up

A thorough history and physical examination is critical in the initial evaluation of mediastinal masses, supplemented by laboratory and imaging studies. It is not uncommon to find testicular masses on imaging while investigating mediastinal masses. A careful history regarding any testicular swelling, undescended testes or previous scrotal surgery should be elicited, particularly in young males. History regarding early myasthenic symptoms like ptosis or dysphagia should also be elicited. Physical examination should include scrotal examination, abdominal examination for retroperitoneal masses and supraclavicular fossa examination.

4.1 Tumor Markers

Alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (beta-HCG) are frequently elevated in germ cell tumors. AFP is elevated in 60% to 80% of nonseminomatous germ cell tumors (NSGCT) and beta-HCG is raised in 10% of seminomas and 30% to 50% of NSGCT [4]. While the absence of elevated tumor markers does not preclude the diagnosis of germ cell tumors, grossly elevated tumor markers clinch the diagnosis and may obviate the need for biopsy confirmation. Lactate dehydrogenase (LDH) is a marker of cellular proliferation and is elevated in tumors with brisk mitoses, particularly so in lymphomas [5]; however, it is not very specific.

4.2 Radiology

Large mediastinal masses can be identified on chest radiography as a soft tissue opacity with loss of borders of normal mediastinal structures (silhouette sign). However, once an abnormality is identified on X-ray, cross-sectional imaging is mandatory to further characterize the lesion and guide further management. Computed tomography with intravenous (IV) contrast is the imaging modality of choice. It provides detailed information regarding the location, size, relationship to other structures and tissue characteristics, like presence of fat, fluid or calcifications (e.g., teratoma) (Fig. 1). Very often in mediastinal masses, characteristic imaging features help identify the primary pathology and guide further management without the need for an invasive biopsy.

Magnetic resonance imaging (MRI), although not routinely performed, may be useful in certain specific scenarios. It is superior to CT in distinguishing cystic from solid masses and infiltration of vascular structures [2]. MRI

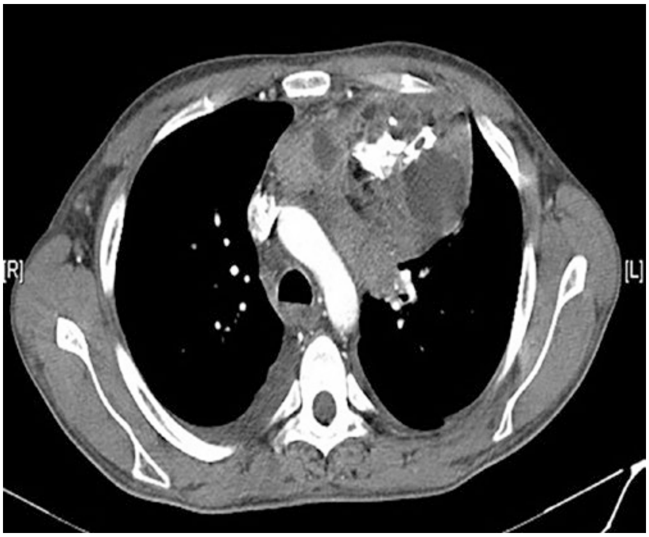

Fig. 1 Mediastinal teratoma

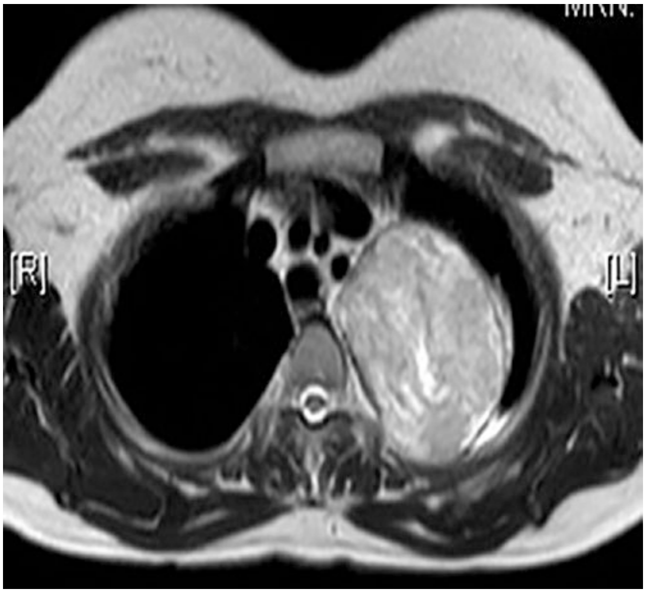

Fig. 2 MRI of posterior mediastinal neurogenic tumor

chemical shift imaging can be used to differentiate thymic hyperplasia from thymoma in adult patients [6]. MRI of the dorsal spine is occasionally warranted to evaluate extension of posterior spinal masses into neural foramina or spinal canal (Fig. 2).

18-FDG PET-CECT is mandated in the staging and monitoring of treatment response in lymphoma and is also occasionally used in the post chemotherapy response evaluation of seminomatous germ cell tumors. Recent reports suggest that it may also be useful in the evaluation of thymic neoplasms, actually predicting the WHO type accurately in 85% [7]. However, it is important to bear in mind that FDG-PET can be misleading, given that the normal thymus, hyperplastic thymus and inflammatory lesions in the mediastinum are all often FDG-avid [8].

4.3 Pathology/Tissue Diagnosis

Not all lesions in the mediastinum warrant a biopsy. Mediastinal masses with characteristic clinical symptoms like myasthenia gravis, pure red cell aplasia or hypogammaglobulinemia and characteristic radiological findings do not require biopsy confirmation before definitive treatment. The decision to biopsy or not becomes difficult when there is a clearly resectable anterior mediastinal mass but the clinical scenario does not allow definitive distinction between a lymphoma or thymoma. Tissue diagnosis is essential to characterize lymphomas and to avoid unnecessary surgery. On the other hand, a biopsy from an encapsulated thymoma carries the risk of tumor seeding along the needle tract and into the pleural cavity [9]. An extrapleural route with a coaxial needle system is the preferred approach to avoid seeding and dissemination of tumor into the pleural cavity. Biopsy techniques include CT-guided transthoracic needle biopsy [10], video-assisted thoracoscopic surgery (VATS), mediastinotomy and open surgical biopsy, with transpleural approaches being the least preferred. In case of posterior mediastinal masses, most are of neurogenic origin and can be characterized by MRI, biopsy being required rarely.

However, the dictum remains, “when in doubt confirm the diagnosis with a biopsy.” Histopathological confirmation is warranted in cases where diagnosis cannot be confirmed by tumor markers or radiology, surgery is not the primary modality of management, the lesion is unresectable or when systemic therapy is required.

5 Management

5.1 Thymoma

Thymic neoplasms are the most common tumors of the anterior mediastinum. They arise from the thymus, a lymphoepithelial organ, the functioning of which is vaguely understood. The thymus is known to play a role in T lymphocyte maturation in early age. Maximum size is achieved at the end of puberty and thereafter, it slowly involutes [11]. Histologically, it is divided into the outer cortex and inner medulla and is mainly composed of thymocytes, lymphocytes and epithelial stroma. Epithelial cells are further subtyped into six.

Thymomas are predominantly seen in middle and old age. In contrast to its developmental pattern, as the gland involutes, the incidence of malignancy increases [12]. The overall incidence of thymoma is 1.5 per million person years, as per the SEER (Surveillance, Epidemiology and End result) database [13]. Over 90% of thymomas are found in the anterosuperior mediastinum. They may also occur in ectopic thymic tissue, most commonly the lower neck, retrocarinal or aortopulmonary window region [14].

5.1.1 Classification

Numerous classification systems have been developed for thymomas over the years. Most of them are of historical value and have little clinical significance. Rosai and Levine, in 1976, developed a classification based on cellular components of the tumor. It had three subtypes: epithelial, lymphocytic and mixed (lymphoepithelial). In this classification, the epithelial type was considered malignant and the lymphocytic type, benign [15]. In 1985, Marino and Muller-Hermelink proposed another classification, based on thymic site of origin: cortical, medullary and mixed thymomas [16]. Later in 1999, Suster and Moran proposed another classification based on morphologic features of differentiation. Here, they were classified into three types: thymoma, atypical thymoma and thymic carcinoma based on the degree of cellular atypia [17].

The World Health Organization (WHO) attempted to organize the pathological classification of thymic tumors and introduced a new nomenclature which subclassified thymomas into types A, AB, B1, B2, B3 and thymic carcinomas. The fourth edition proposed in 2015 remains the most widely used classification system. Thymomas, regardless of subtype, should be considered as malignant neoplasms. Subtypes A, AB and B1 belong to the relatively benign end of the spectrum with lower incidence of invasiveness, locoregional spread and metastasis. Types B2, B3 and thymic carcinomas are more likely to present with locoregionally advanced or metastatic disease [18]. The presence of invasion through the capsule into the surrounding structures dramatically increases the rate of metastases, particularly to the pleural cavity and lung [19]. This may occur despite a cytologically benign appearance. Thymic carcinomas are rare, aggressive tumors which portend an extremely poor prognosis. They have much higher rates of cellular atypia and genetic imbalance as compared to thymomas.

5.1.2 Staging System

Masaoka et al. proposed a surgical staging system for thymomas in 1981 which was predictive of 20-year survival [20]. It was later modified in 2011 and renamed the Masaoka–Koga staging system [21]. This is currently the most popular clinical and pathological staging system and is endorsed by the International Thymic Malignancy Interest Group (ITMIG). The UICC TNM staging system, which was brought into practice in January 2018, still awaits clinical validation Staging can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 428, Chapter no. 35, Thymus Table: Definition of TNM and AJCC prognostic stage groups which can be accessed at https://emedicine.medscape.com/article/1999313-overview

5.1.3 Presentation

A significant proportion of mediastinal masses are diagnosed incidentally, on routine chest imaging performed for some other reason [13, 22]. The rest, present with symptoms related to local compression, infiltration, paraneoplastic syndromes or rarely metastases. Common presenting symptoms are heaviness in the chest, pain, cough and respiratory symptoms like dyspnea on exertion. When the tumor increases in size it starts compressing/invading adjacent structures and causing symptoms as mentioned in the previous section. In addition to the symptoms commonly caused by anterior mediastinal masses, thymic neoplasms are characteristically associated with a number of systemic syndromes. They may be classified as autoimmune disorders, endocrine disorders, blood dyscrasias and neuromuscular syndromes. A detailed description of all these associations is beyond the scope of this chapter and the discussion will be limited to the most common ones.

Myasthenia gravis is the most commonly associated autoimmune disorder. In one series myasthenia gravis (MG) was the third most common presenting symptom after asymptomatic presentation and chest pain [17]. Around 24% to 40% of thymoma patients develop MG [23], while 15% to 20% of MG patients develop thymoma. MG is caused by the presence of autoantibodies to postsynaptic nicotinic acetylcholine receptors. This manifests as muscle weakness leading to ptosis, diplopia, dysarthria, dysphagia, etc. Severe cases may cause respiratory weakness and crisis. The mainstay of treatment is anticholine esterase mimetic agents like pyridostigmine and immunosuppressive drugs like corticosteroids and azathioprine. In severe cases, intravenous immunoglobulins and plasmapheresis may be used. The role of thymectomy in patients with MG is subject to debate, with varying levels of remission reported. The randomized MGTX trial demonstrated benefit with thymectomy in patients with antibody positive MG without a thymoma, with patients undergoing thymectomy having lower requirement for immunosuppression and decreased hospitalization [24]. However, whether surgery is beneficial in patients with MG and thymoma is unclear.

Pure red cell aplasia (PRCA) is an autoimmune disorder causing anemia due to the absence of red cell precursors in the bone marrow. Around 10% of patients with PRCA may have an associated thymoma, but the incidence of PRCA in a known case of thymoma is very rare [25] Thymectomy helps in remission in only around 30% of patients with PRCA and a thymic mass [20].

Hypogammaglobulinemia is seen in 6% to 11% of patients with thymoma. Both cellular and humoral immunity are affected. Patients usually present with recurrent chest infections or sinusitis. Role of thymectomy in this syndrome is doubtful [26] with very low remission rates, long-term immunoglobulin therapy being the only treatment option.

5.1.4 Investigations

Contrast-enhanced computed tomography (CECT) of the thorax is the preferred investigation for thymic neoplasms. It gives a clear picture about the extent of disease and planes with surrounding structures (Fig. 3). In addition, it provides information about the presence of pleural and parenchymal deposits, the most common sites of metastases. Thymoma classically appears as a homogenous, well defined mass, enhancing with contrast [27]. In most cases, CECT of the thorax provides adequate information to characterize the lesion and decide regarding resectability. In more advanced cases with infiltration of adjacent vascular structures, MRI may be a useful tool [28] (Fig. 4). A few studies have used diffusion-weighted (DW-MRI) [29] and 18-FDG PET CECT [30] to differentiate low- and high-grade thymic neoplasms and have shown good correlation with survival as well (Fig. 5). However, this has yet to prove benefit in clinical practice.

An anterior mediastinal mass with characteristic radiological features of a thymoma presenting with associated syndromes like myasthenia gravis or PRCA does not require histopathological confirmation. In case of any diagnostic dilemma, or in cases which may require multimodality management, it is better to obtain tissue diagnosis before starting treatment. CT-guided biopsy through an extrapleural route is the preferred method.

Anti-acetylcholine receptor (anti-AchR) antibody levels should be checked in all patients with suspected thymic neo-

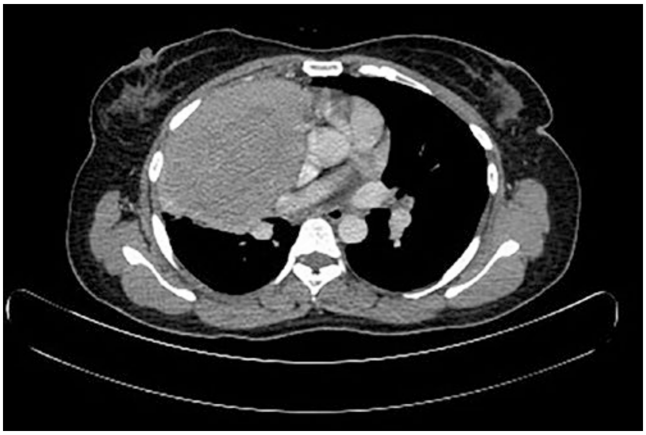

Fig. 3 Thymoma

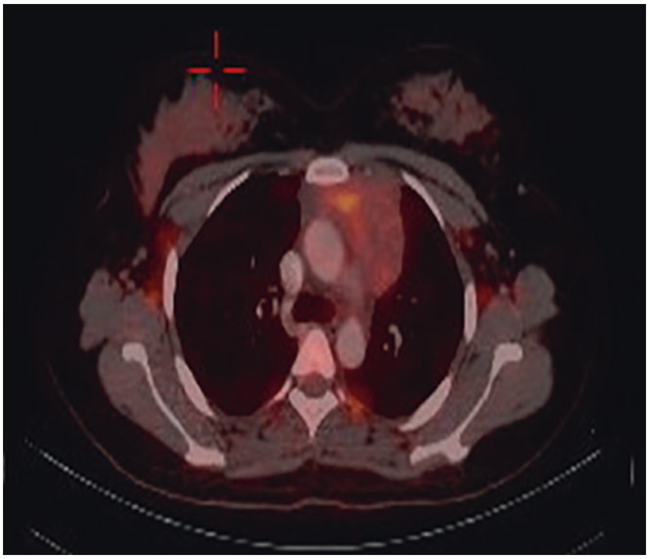

Fig. 5 PET CECT of thymoma showing pleural drop metastasis

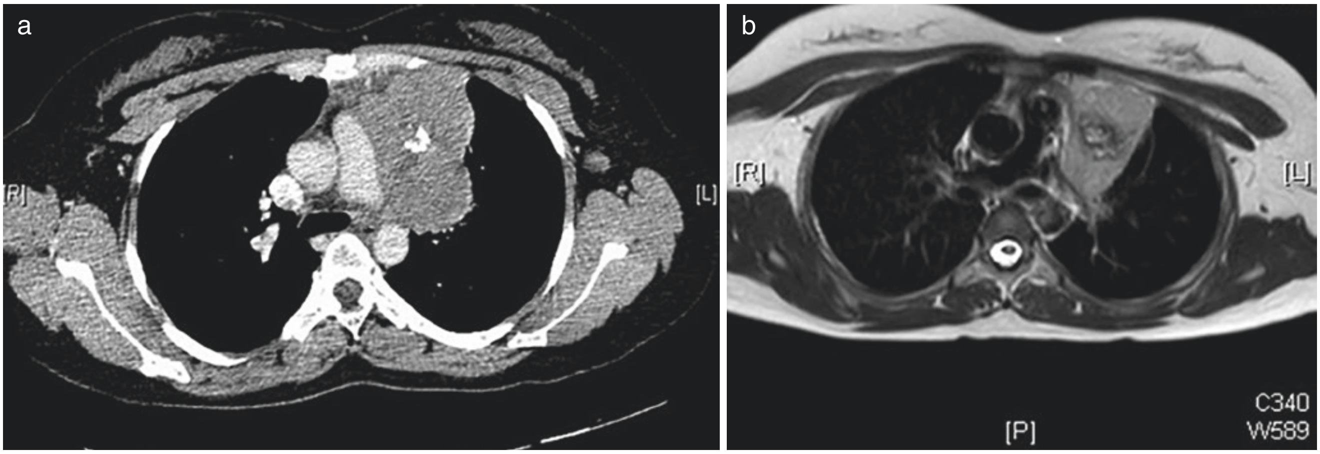

Fig. 4 (**a**) CT scan of thymoma with suspected infiltration of pulmonary conus. (**b**) MRI shows no evidence of infiltration of pulmonary artery

plasms [31]. Presence of antibodies helps in clinching the diagnosis and may help avoid a biopsy. All patients with MG may not have overt symptoms and it is important to diagnose such cases and start medical management before embarking on surgery. Thymectomy in previously undiagnosed cases of MG may cause exacerbation of MG and myasthenic crisis.

5.1.5 Management

Stage I/II

Surgery is the mainstay of treatment for early stage thymoma (Masaoka I/II). In well encapsulated and resectable tumors, primary surgery is the preferred treatment option. The extent of surgical resection involves en bloc resection of the tumor mass with all fibro-fatty tissue anterior to the pericardium between both phrenic nerves bilaterally and from the hyoid to the diaphragm craniocaudally. Dissection of the first echelon of draining lymph nodes, i.e., pericardial, aortopulmonary and paratracheal, is recommended by ITMIG. Completeness of resection (R0) is an important prognostic factor and confers improved survival [32]. Every attempt should be made to resect the tumor without any breach of the capsule, along with the entire thymus and any adjacent structures which are infiltrated. All efforts should be made to preserve the phrenic nerves, at least on one side. Involvement of the phrenic nerve can be predicted by an elevated hemidiaphragm on preoperative imaging and should be kept in mind during surgery, so that extra precautions can be taken to safeguard the contralateral nerve. The traditional approach to thymic surgery has been via a median sternotomy, and it still remains the go-to approach in difficult cases. Minimally invasive approaches, both VATS and robotic are gaining in popularity and several series have shown no difference in R0 resection rates or local recurrence rates between the two approaches [33]. Length of hospital stay is shorter in the minimally invasive surgery group with no difference in major perioperative complications [34].

Stage I thymic neoplasms do not require adjuvant treatment, regardless of histology. Adjuvant treatment in stage II is a matter of debate. Patients with Stage II and R0 resection did not benefit from postoperative radiation therapy (PORT) in the earlier trial [35]. In fact, the Chinese Alliance for research in Thymomas (ChART) showed a detrimental effect of PORT in patients with an R0 resection. However, patients with R+ resection had better overall survival (OS) and disease-free survival (DFS) with PORT [36].

Stage III/IV

Stage III and IV thymic neoplasms require multimodality management. Surgery should be attempted wherever R0 resection is possible. In patients with borderline resectability, induction chemotherapy should be considered. Combination chemotherapy with cisplatin and anthracyclines has shown modest pathological response as well as better R0 resection rates [37]. Whenever multimodality treatment is anticipated in a patient planned for surgery, it is preferable to administer the chemotherapy before surgery in view of the improved tolerability and a higher R0 resection rate. Adjuvant radiotherapy has demonstrated a survival advantage in Stage III and IV thymomas, particularly after a macroscopic complete resection [38]. The ChART trial showed improvement in survival in margin positive resected thymomas [27].

The role of debulking surgery in thymoma is controversial. A number of series and a meta-analysis have shown marginal benefit with debulking surgery over biopsy alone [39, 40]. However, most of these series are retrospective and have an inherent selection bias, making it difficult to draw definitive conclusions. Similarly, the role of surgery in recurrent disease is also questionable with a few series showing marginal benefit with resurgery [41].

In unresectable lesions, concurrent chemoradiation with radiation doses up to 60 Gy can be given [42]. Intensity-modulated radiotherapy (IMRT) with respiratory gating is the preferred technique. Systemic therapy with combination chemotherapy can be attempted in metastatic or recurrent disease [43], although there is no strong evidence in support. A number of targetable mutations like tyrosine kinase (TK), c-KIT and the more recent PD-L1 have been identified in thymic neoplasms [43, 44]. However, early studies have not been able to demonstrate a significant benefit, and further research is warranted.

5.1.6 Prognosis

As in any other malignancy, the two most important outcomes considered after treatment of thymic neoplasms are recurrence and overall survival. As far as recurrence is concerned, the WHO histological type, Masaoka stage, resection status, tumor size and postoperative treatment are important determining factors. In one study, after a median follow up 105 months, a recurrence rate of 1.5% to 7.5% was seen in Masaoka Stage I and II, whereas it was 30% in stage III and 80% in IVa, respectively. B2 and B3 histological types have higher chances of recurrence compared to A, AB and B1 [16]. On multivariate analysis, tumor size more than 4 cm has been found to be an independent factor negatively impacting recurrence-free survival (RFS) [44]. As mentioned in the previous section, the ChART study showed improved recurrence-free survival with radiotherapy after R+ resection and in advanced stages (III/IV). A retrospective analysis of the ITMIG database showed 5- and 10-year survival of 95% and 86% with surgery and PORT in stage II and III thymoma, respectively [45]. In a multi-institutional trial, 5-year overall survival rate after total resection, subtotal resection, and inoperability was 93%, 64%, and 36%, respectively, in stage III and IV thymoma [32].

6 Mediastinal Germ Cell Tumors

Mediastinal germ cell tumors (GCT) are derived from primitive germ cells that fail to migrate completely during early embryogenesis. The mediastinum is the most common extragonadal primary site for GCT. GCTs comprise 10% to 15% of anterior mediastinal masses. They are seen more commonly in males and in the third decade of life.

Although histologically similar to their gonadal counterparts, they have a more aggressive biology and poorer prognosis. When a malignant mediastinal germ cell tumor is diagnosed, primary gonadal GCT must be excluded by scrotal and abdominal examination and a scrotal ultrasound.

GCTs are a heterogeneous group and are classified into benign teratoma, malignant seminoma and nonseminomatous germ cell tumor (NSGCT). Serologic tumor markers like alpha-fetoprotein (AFP), human chorionic gonadotropin (beta-HCG) and lactate dehydrogenase (LDH) are helpful in diagnostic differentiation.

6.1 Teratoma

Benign teratomas are the most common mediastinal GCT and arise from one of the three primitive germ cell layers [46]. Mature teratomas are composed predominantly of ectodermal components like skin, hair or tooth like structures and less commonly mesodermal components like fat, cartilage and bone. Immature and malignant teratomas contain fetal and neuroendocrine tissue and carry a poor prognosis. Rarely, mature teratomas may undergo malignant transformation with a focus of sarcoma or carcinoma.

Mature teratomas occur in children and young adults and are usually asymptomatic. They present as an encapsulated mass in the anterior mediastinum and may protrude to one side of the midline. Radiologically, a uniloculated or multiloculated cystic lesion containing fluid, soft tissue, calcium and/or fat attenuation in an anterior mediastinal mass is a characteristic finding of a teratoma (see Fig. 1). Calcifications are seen in up to 30% of these tumors and they may be focal or rim like. In a small subset of cases mature teratomas may appear as cystic lesions without fat or calcium [5]. Tumor markers are normal in these patients. Complete surgical resection is the treatment of choice [47]. Radiotherapy and chemotherapy play no role in management of teratomas.

6.2 Seminoma

Seminomas are uncommon in their pure form. They are seen in men who are in their second to fourth decades of life. Clinically, patients have dyspnea, substernal chest pain and up to 10% of them present with superior vena cava syndrome [48]. Pure seminomas have normal AFP levels and beta-HCG may be elevated in 10%. Radiologically, seminomas are bulky homogenous masses which usually do not invade locally but metastasize to lymph nodes and calcifications are rare.

Pure seminomas fall under the Intermediate Risk category of the International Germ Cell Consensus Classification and the intent of treatment should be curative even in patients with visceral metastases. These are very radiosensitive tumors and for many years, radiation had been used in the primary setting or adjuvant setting to achieve local control. But, due to large radiation portals and high recurrence rates at distant sites, cisplatin-based combination chemotherapy is currently considered as first line therapy [49].

Small localized tumors may be treated with radiation alone and for locally advanced disease, the most common presentation, the preferred treatment is systemic chemotherapy (cisplatin and etoposide) [50]. The response to chemotherapy is usually excellent, with tumor markers normalizing and even large tumors shrinking dramatically to small plaque like lesions [51]. The role of surgery in the definitive management of seminomas is subject to debate. Although surgery can extirpate the residual disease and give an idea as to the completeness of response to chemotherapy, surgery itself may be technically demanding due to the dense desmoplastic reaction and fibrosis after chemotherapy. Most often, no residual disease is found in the resected mass. Hence, the debate whether it is worthwhile subjects the patient to the morbidity of a technically demanding surgery. Another frequently used strategy in patients with normalized tumor markers is to follow up the residual mass with PET CECT imaging and CT guided biopsy and consider for resection only if there is FDG uptake or biopsy shows residual disease or teratoma [52]. If residual disease is present and deemed unresectable, radiotherapy is the modality of choice, since these tumors are exquisitely sensitive to radiotherapy [53]. Surgical debulking of large seminomas has shown no benefit in improving survival [54].

6.3 Nonseminomatous Germ Cell Tumors (NSGCT)

NSGCTs comprise a diverse group including embryonal cell carcinoma, yolk sac tumors, endodermal sinus tumors, choriocarcinoma and mixed germ cell tumors. These are malignant tumors and are mostly symptomatic, with 80% being metastatic at the time of diagnosis. NSGCT is uniquely associated with hematological malignancies and 20% of them have Klinefelter's syndrome [55]. Tumor markers (AFP, beta-HCG, LDH) are elevated in majority of the cases and are important in establishing a diagnosis. AFP is high in embryonal carcinoma or endodermal sinus tumor.

Radiologically, NSGCTs are large, irregular heterogeneous masses with areas of necrosis, hemorrhage or cyst formation. They invade adjacent structures and may metastasize to lymph nodes and distant organs. Accompanying pleural and pericardial effusions are not uncommon with these tumors.

The initial treatment of NSGCT is cisplatin-based chemotherapy. Various combinations of cisplatin with ifosfamide, vinblastine, bleomycin or etoposide have been studied. Complete remission rates range from 40% to 60% in most series [49, 56, 57]. Four cycles of VIP (vinblastine, ifosfamide and cisplatin) is the preferred regimen over BEP (bleomycin, etoposide and cisplatin) due to increased risk of bleomycin induced pulmonary toxicity in patients with underlying lung disease or in patients requiring thoracotomy or sternotomy for residual lesions [58]. The efficacy of both the regimen appears to be similar. Surgical resection for any residual mass, which could represent either a teratoma or residual disease, is indicated when the tumor markers normalize. Salvage chemotherapy is administered to patients with persistently high tumor markers.

Primary mediastinal NSGCTs fall into the poor risk category of International Germ cell Consensus classification and have 40% to 50% 5-year survival which is lower compared to their gonadal counterparts.

Growing teratoma syndrome is a rare clinical phenomenon seen in patients with NSGCT at the primary or metastatic sites. It was described by Logothetis in 1982 [59] as masses of NSGCT enlarging despite systemic chemotherapy and normalization of tumor markers, with exclusive presence of mature teratoma and no viable germ cell component. The incidence ranges from 1.9% to 7.6% in all NSGCT [60], with the most common site being retroperitoneum. In primary mediastinal NSGCT, growing teratoma syndrome is rare with one series reporting 2.6% [61]. Early diagnosis of this clinical entity is important due to the complications caused by mechanical compression of the surrounding structures by the enlarging mass. As it comprises mainly mature teratomatous component, chemotherapy or radiotherapy is ineffective. Complete surgical resection is the treatment of choice and carries excellent prognosis. Recurrence rates following complete resection are low, around 4%, whereas with incomplete resection, recurrence ranges around 83% [62].

7 Posterior Mediastinal Tumors

A majority of posterior mediastinal tumors are of neurogenic origin. Most arise from the sympathetic trunk or intercostal rami and are Schwannomas or neurofibromas. In general, neurogenic tumors are benign with approximately 30% associated with von Recklinghausen syndrome [63]. Rarely, Schwannomas may arise from the vagus nerve in the middle mediastinum [64]. Most of them are asymptomatic and are diagnosed incidentally. However, they may erode adjacent osseous structures and extend through vertebral foramina forming dumbbell tumors. Symptoms, when they occur, are due to compression of the tracheobronchial tree, nerve roots or the chest wall. The incidence of malignancy in neurogenic tumors is rare with most of them occurring in the background of neurofibromatosis [65].

The initial radiological investigation of choice is CECT thorax with characteristic features obviating the need of a biopsy. MRI may help in better characterization and in identifying intraspinal extension or neural involvement (see Fig. 2).

Asymptomatic and small tumors with no significant compression over adjacent structures may be observed. In symptomatic patients, complete surgical resection without breach of the capsule is the treatment of choice. A minimally invasive approach is preferred where possible. In case of intraspinal extension, a combined approach along with a neurosurgical team may be required. While the results of surgery are generally good, the prognosis after surgery for malignant tumors remains poor [66]. Most require postoperative radiotherapy, but there is no definite evidence of benefit with adjuvant chemotherapy [63].

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Esophageal Cancer

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Abbreviations

ADC	Adenocarcinoma
BE	Barrett's esophagus
CECT	Contrast-enhanced computed tomography
DLCO	Diffusion capacity of lung for carbon monoxide
EBRT	External beam radiation therapy
EMR	Endoscopic mucosal resection
EUS	Endoscopic ultrasonography
FEV1	Forced expiratory volume in first second
GERD	Gastroesophageal reflux disease
HDI	Human development index
HPV	Human papilloma virus
ILRT	Intraluminal brachytherapy
IMRT	Intensity-modulated radiation therapy
LTA	Left thoracoabdominal
MIE	Minimally invasive esophagectomy
NACRT	Neoadjuvant treatment with chemoradiotherapy
NACT	Neoadjuvant treatment with chemotherapy
NART	Neoadjuvant radiotherapy
PET	Positron emission tomography
PFT	Pulmonary function test
SCC	Squamous cell carcinoma
THE	Transhiatal esophagectomy
UGIE	Upper gastrointestinal endoscopy

1 Introduction

Esophageal cancer ranks seventh in terms of incidence worldwide with 572,000 new cases and sixth in overall mortality [1]. There has been a steady increase in new cases of esophageal cancer with approximately 70% occurring in men. Highest rates of incidence have been reported from East Asia followed by Southern Africa [2]. Majority of them lie in the "esophageal cancer belt" which extends from North-East China to the Middle East. Adenocarcinoma (ADC) and squamous cell carcinoma (SCC) being the most common histological types of esophageal cancer vary in their distribution, and melanoma, small cell carcinoma, sarcoma or lymphoma constitute a small proportion (1%–2%) of these cancers. In countries with a high human development index (HDI), there is higher incidence of adenocarcinoma of the esophagus, whereas in low HDI countries like India, SCC is more common [3]. The incidence peaks in the sixth decade in most parts of the world. In India, esophageal cancer is the sixth most common cause of cancer related death and the North-East region of India reports the highest incidence [4].

2 Risk Factors

Esophageal squamous cell carcinoma and adenocarcinoma differ in their epidemiology, pathogenesis and biological behavior. Pathophysiology of SCC is believed to be a precursor lesion of epithelial dysplasia progressing to severe dysplasia to carcinoma in situ and finally to invasive carcinoma [5]. ADC, in contrast, is usually seen in patients with persistent gastroesophageal reflux disease (GERD) and intestinal metaplasia (metaplasia–dysplasia–neoplasia sequence) [6].

Major risk factors for SCC are tobacco/smoking, alcohol consumption, poor nutritional status, caustic injury, consumption of hot beverages and possibly human papilloma virus (HPV) infection. Smoking and alcohol have a synergistic effect and is related to carcinogenic ingredients like polycyclic aromatic hydrocarbons, nitrosamines, aldehydes and

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their derivatives [7]. Local risk factors in India like betel quid chewing, hookah, snuff, hot salted tea and red chilies have been implicated in carcinogenesis. HPV is reported to be associated with SCC in high incidence areas but exact role in pathogenesis needs further study [8].

The risk factors of ADC include obesity, GERD, cigarette smoking, Barrett's esophagus (BE), male sex and diet low in vegetables and fruit. BE is strongly associated with GERD and the risk of developing ADC is 0.1–0.5% per year. The risk increases with increasing length of Barrett's [9]. Deficiency of micronutrients such as vitamin A, E, C, riboflavin, zinc and selenium also contribute to development of esophageal cancer.

Genetic alterations such as mutations in p53, cyclin D1 and cell cycle regulatory proteins have been associated with development of esophageal cancer [10]. In high incidence areas like China, genetic susceptibility (familial aggregation) to ESCC has been reported [11]. Tylosis, a hereditary disorder, involving hyperkeratosis of the palms and soles, has a high risk of esophageal cancer [12].

3 Clinical Presentation

Progressive dysphagia or odynophagia are the most common presenting symptoms of esophageal cancer. Unintentional weight loss (more than 10% of normal body weight in 6 months) is seen mostly in ESCC patients and is not a frequent finding in EADC. Some symptoms develop late in the course of the disease like chest pain or back pain when swallowing, supraclavicular lymphadenopathy, hoarseness from recurrent laryngeal nerve involvement, cough or sudden onset of hiccups. Screening endoscopy in Japan and Korea picks up early asymptomatic disease, but in India, disease is mostly locally advanced at the time of presentation.

4 Diagnosis and Staging

1. Barium swallow—Though barium swallow is sometimes used as the initial assessment tool in peripheral hospitals, its clinical utility is questionable. A normal barium swallow does not preclude the need for an upper gastrointestinal endoscopy (UGIE) as early mucosal lesions may get missed with a barium swallow; in an abnormal barium swallow, an UGIE would be required in any case to map the disease and biopsy the lesion. Therefore, it provides no additional information, nor does it change the management in any way. It is therefore not indicated in patients with suspected esophageal cancer.
2. Upper GI endoscopy—This remains the preliminary investigation of choice for patients with dysphagia. The endoscopy should be thorough, and should have a clear mention of the location of the tumor, extent of involvement, level of the cricopharynx and the gastroesophageal junction. A minimum of 6 to 8 biopsies is recommended to minimize the need for repeat endoscopies. Brush cytology has shown a correlation of 80% in most studies and may be explored for screening or rapid diagnosis, and is of value in predominantly stricturous lesions [13].
3. Radiology.
   (a) Contrast-enhanced computed tomography (CECT) thorax and abdomen—A CECT scan is the initial imaging modality to stage esophageal cancer. It is effective in assessment of the T stage, invasion of surrounding structures and screening liver, and lung for distant metastases. However, it is less accurate for nodal assessment.
   (b) PET-CT—^{18}FDG positron emission tomography (PET) provides incremental staging information, especially when combined with CT scan. The diagnostic accuracy increases to 92% when both modalities are used. Distant metastases are best detected by PET-CT and it can change the clinical management in a significant number of patients [14]. It should be included routinely in diagnostic algorithm of esophageal cancer staging. PET-CT has also shown encouraging results in assessing the response to induction therapy [15]. However, it might be less effective in assessment of response to neoadjuvant chemoradiation than to neoadjuvant chemotherapy.
4. Endoscopic ultrasonography (EUS) is used for refining locoregional staging. It is superior to CECT with regards to assessment of depth of tumor invasion and regional nodal status. It helps to delineate various layers of the esophageal wall and has high sensitivity and specificity for defining the T stage in esophageal cancer. However, with the acceptance of neoadjuvant chemoradiotherapy or chemotherapy as the treatment of choice in localized esophageal cancer, the role of EUS is restricted to very early disease (where T1N0 cancers may be operated without neoadjuvant treatment) or in patients with borderline resectability. Advanced (T4) disease is detected better with EUS than early (T1) lesions. High-frequency probes (20–30 Mhz) increase the accuracy for T1 and T2 tumors [16]. EUS has the advantage of the possibility to perform FNA during the procedure. Sensitivity and specificity of EUS improves from 85% to 96% in evaluating N stage with addition of FNA from nodes [17]. EUS may not be technically feasible in stenotic lesions. Its role in restaging after neoadjuvant therapy is limited, as it cannot reliably differentiate between fibrosis and residual or recurrent disease.
5. Bronchoscopy is essential for assessing trachea-bronchial tree involvement in upper and middle third esophageal disease prior to starting treatment, especially in patients with bulky disease on axial imaging. It is more sensitive than conventional imaging modalities to diagnose early involvement of the tracheobronchial tree.

6. Minimally invasive staging—The role of laparoscopy and thoracoscopy in preoperative staging is being investigated. Some studies have shown that detection of advanced disease (<1 cm lesions) and positive lymph nodes, is better with these modalities as compared to noninvasive staging [18]. Staging laparoscopy has a role in the staging algorithm for esophageal and gastroesophageal adenocarcinoma, picking up occult metastases in 20% to 40% of the patients even after comprehensive radiological staging [19].
7. Tumor markers—Various biomarkers including immunohistochemical markers, serum tumor markers and miRNA markers have been evaluated in diagnosis and prognosis of esophageal cancer. CEA, p53 antibody, SCC-Ag, Cyfra21–1 and VEGF-C have been studied for their potential in aiding diagnosis of esophageal carcinoma, but they are not yet recommended for use in routine practice [20].
8. Functional evaluation with echocardiography and pulmonary function test (PFT) is useful in most patients planned for radical treatment. Forced expiratory volume in first second (FEV1) and diffusion capacity of lung for carbon monoxide (DLCO) are important predictors of pulmonary complications and values of less than 40% are associated with high risk.

5 Staging

The eighth edition of American Joint Committee on Cancer (AJCC) staging of the esophageal cancers came into effect in 2017 and included certain changes from the seventh edition: [21].

- Separate classifications for clinical (cTNM), pathologic (pTNM) and postneoadjuvant (ypTNM) stage groups. The rationale for this addition was the absence of equivalent categories peculiar to the post neoadjuvant state (ypT0N0-3 M0 and ypTisN0-3 M0) and markedly different survival profiles. Adenocarcinoma and squamous cell carcinoma are classified separately in clinical and pathological staging, but ypTNM groupings are identical for both cell types.
- Subclassification of T1 into 1a and 1b.
- Definition of subtype (squamous/glandular) and grading of cancers (% in glands).
- Definition of location: Epicenter of the tumor is used to define the location in eighth, edition whereas it was the upper edge of the cancer in seventh edition.
- Redefinition of gastroesophageal tumors: Adenocarcinomas with epicenter ≤2 cm into the gastric cardia will be staged as esophageal cancers and those extending further (>2 cm) will be staged as stomach cancers.

With the new staging system, groups are more homogenous with respect to prognosis and separation of survival curves. However, for future staging, more refinement in terms of (1) integration of genomics; (2) precision cancer care with targeted therapy; and (3) pathological staging of endoscopically resected cancers are planned to be explored.

6 Patient Optimization

A detailed nutritional assessment and rehabilitation for all patients is part of the initial management of esophageal cancer. Patients with pronounced dysphagia are often malnourished, especially in those with squamous esophageal cancer. Enteral feeding is the preferred route of choice for nutritional supplementation. Endoscopic or fluoroscopic-guided nasogastric tube insertion may be needed for severely dysphagic patients (grade III/IV) at risk of malnutrition.

Pulmonary rehabilitation should be initiated early in the management of esophageal cancers. It is necessary for all patients planned to be treated with radical intent and those with compromised lung function. Incentive spirometry exercises and adequate rehabilitation, significantly reduces the rate of pulmonary complications. Cessation of smoking must be stressed in pretreatment counseling.

7 Management

A multidisciplinary team approach is recommended for treatment of esophageal and gastroesophageal (GEJ) cancers. Standard of care for locoregionally advanced esophageal cancers (cT3,4/N+) is a multimodality approach with integration of chemotherapy, radiotherapy and surgical resection, whereas a single modality may be sufficient for early disease (cT1,2 N0).

Factors deciding treatment include:

- Location of the disease.
  - Cervical esophageal cancer and upper third lesions within 5 cm of cricopharynx are preferred to be treated with concurrent chemoradiation or radical radiotherapy [22].
  - For resectable middle third, lower third and GEJ cancers, surgery is the most effective treatment.
- Stage of the disease.
  - Early stage cancers (T1–2, N0) are treated with single modality—either endoscopic resection (EMR/ESD for very early disease) or surgery.
  - Locally advanced disease (T3–4a or N+) receive multimodality treatment-neoadjuvant therapy followed by surgery or definitive chemoradiation.

- Patients with metastatic disease require palliation of symptoms with either palliative radiation, esophageal stenting or palliative chemotherapy.

7.1 Endoscopic Treatment

Early superficial esophageal cancers may be managed with either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). Indications for endoscopic treatment include (1) Intramucosal lesion (T1a); (2) Diameter of lesion less than 2 cm or less than one-third of the circumference of the esophagus; (3) Absence of nodal involvement [23]. EMR constitutes elevation of the lesion, placement of a metal wire snare and resection using high-frequency diathermy whereas, in ESD, the mucosa is excised using a high-frequency diathermy knife, and dissection is done in the submucosal plane beneath the lesion. An ideal candidate for EMR or ESD would be a T1a well-differentiated lesion, less than 2 cm in diameter, with no ulceration, no lymphovascular or nodal involvement. In these selected cases, endoscopic treatment is gaining equal cure rates in specialized centers [24]. pT1a and pT1b tumors are associated with low risk of nodal metastases (1% and 3%, respectively) and it is assumed that ESD and EMR can achieve similar outcomes as with open surgical resection. Local recurrence rates are high in cases of positive margins or piecemeal resection. Endoscopic surveillance at 6–12 monthly intervals is desirable to detect residual or recurrent tumor and metachronous lesions.

7.2 Surgery

Traditionally, the standard treatment for resectable esophageal cancers is esophagectomy. However, survival is not satisfactory with surgery alone although there have been advances in new surgical techniques and perioperative care. Now, surgery is part of the multimodal treatment approach to improve outcomes.

Indications of surgery include:

(a) Early stage disease (cT1/T2, N0).
(b) Locally advanced disease (T3/T4a, N+) after neoadjuvant treatment.
(c) Residual disease or local recurrence after definitive chemoradiation (salvage esophagectomy).

Principles of surgery are:

(a) To achieve free proximal and distal margins longitudinally and negative circumferential resection margins (CRM). While conventionally a 5-cm margin longitudinally was considered necessary, two retrospective studies have shown that a proximal margin of >3 cm does not yield further survival advantage [25]. A positive CRM is associated with poor prognosis in esophageal cancer patients but the benefit of adjuvant therapy in such setting is still unclear [26, 27].
(b) To perform adequate lymphadenectomy. There is increasing evidence that the number of lymph nodes dissected is an independent prognostic factor after esophagectomy. Traditionally a standard (infracarinal) two-field lymphadenectomy is recommended for most patients with esophageal cancer; in patients with supracarinal nodal involvement, more extensive lymphadenectomy (three field/total mediastinum) may be considered. However, evidence supporting their routine use is lacking.

7.3 Surgical Approach (Table 1)

Surgical approach for esophagectomy depends on the location of tumor, extent of lymphadenectomy planned and expertise of the operating surgeon. The procedure should be least morbid while oncological resection is not compromised.

- For lesions involving upper third and cervical esophagus, surgery is reserved for residual or recurrent disease post chemoradiation and it would entail an extensive procedure of total laryngo-pharyngo-esophagectomy with permanent tracheostomy.
- For lesions involving the middle and lower third of the esophagus, transthoracic esophagectomy with cervical esophagogastric anastomosis is preferred as it provides good access for lymphadenectomy and resection of primary.

Table 1 Types of surgical approach

Surgical approach	Incision	Anastomosis
Transthoracic esophagectomy (TTE)	3 incisions • Laparotomy • Posterolateral thoracotomy • Left supraclavicular	Neck
Transhiatal esophagectomy (THE)	2 incisions • Laparotomy • Left supraclavicular	Neck
Ivor Lewis esophagectomy	2 incisions • Laparotomy • Posterolateral thoracotomy	Thorax
Left thoracoabdominal approach (LTA)	1 incision • Oblique incision extending from abdomen into left thorax	Thorax

- For lesions involving the esophagogastric junction, different approaches may be used like transhiatal esophagectomy (THE), left thoracoabdominal (LTA), Ivor Lewis or transthoracic esophagectomy.

The Ivor Lewis esophagectomy and McKeown procedure (TTE) include a posterolateral right thoracotomy through the fifth intercostal space followed by an esophageal resection with mediastinal and abdominal D2 lymphadenectomy. In TTE and THE, the anastomosis is in the neck, whereas in LTA and Ivor Lewis esophagectomy, the anastomosis is intra thoracic. The procedures involving a thoracotomy (TTE, LTA and Ivor Lewis), allow better clearance of lymph nodes; however, they are also associated with higher rates of pulmonary complications. A randomized trial comparing THE and TTE for adenocarcinoma of the esophagus showed better lymph nodal harvest and trend toward improved long-term survival with TTE but there was increased incidence of pulmonary complications and no significant difference in median or disease-free survival when compared to THE [28]. Similarly a Japanese randomized trial comparing THE with LTA for GEJ tumors failed to show a survival advantage with left thoracoabdominal approach [29]. Two meta-analyses comparing transhiatal to transthoracic esophagectomy showed no difference in disease-free or overall survival; however, most studies in the meta-analyses were retrospective or prospective case series with few randomized trials [30, 31].

Minimally invasive esophagectomy (MIE) with a combined thoracoscopic and laparoscopic approach has been increasingly adopted in recent times to decrease the morbidity and mortality of open esophagectomy. There are three different positions for MIE—prone, lateral and semiprone, based on the surgeon's preference. In a systematic review of studies, morbidity (in terms of blood loss, hospital stay, total complication rate and pulmonary complications) was lower with MIE when compared with open esophagectomy, although all the studies assessed were retrospective [32]. Another prospective, multi-institutional study on MIE, found the stage specific survival to be similar between both the groups [33]; however, it was difficult to fully assess the oncological outcomes of MIE without long-term follow-up. A multicentric, randomized trial comparing open versus MIE demonstrated a significant reduction in pulmonary complications with MIE group [34]. Another randomized trial compared a hybrid minimally invasive approach (laparoscopic abdominal mobilization and open right thoracotomy) with a completely open TTE. The trial confirmed the lower incidence of postoperative complications, mainly pulmonary complications; surprisingly, there was a strong trend (statistically not significant) toward improved overall and disease-free survival in the hybrid MIE arm [35]. Robotic esophagectomy was first started in Netherlands in 2003 and is subsequently being performed in specialized centers across the globe. A case series from Netherlands demonstrated comparable results of robotic esophagectomy to published literature on open surgery, with regards to lymph node yield, extent of resection and survival [36]. The randomized ROBOT trial [37] compared open esophagectomy to the robot-assisted procedure and found overall fewer postoperative complications, decreased blood loss, pulmonary complications, cardiac complications and lower pain. The functional recovery and quality of life measures were also improved with robotic surgery. However, the benefits of robotic esophagectomy over thoracolaparoscopic esophagectomy are uncertain.

7.4 Extent of Lymphadenectomy

Lymph nodal status is one of the most important predictors of survival. The AJCC staging system categorizes regional disease as all periesophageal nodes extending from the lower cervical nodes down to the celiac axis. A minimum lymph node harvest of 15 (12–18) is recommended for adequate staging [38]. In esophagectomy, lymph nodal dissection is most commonly divided into three fields—(1) abdominal field with gastrohepatic and D2 nodes; (2) intrathoracic field with periesophageal, infracarinal nodes and superior mediastinal nodes up to the thoracic inlet; (3) cervical field with nodes along recurrent nerves, supraclavicular and lower deep cervical nodes. Rather than defining the number of lymph nodes to be dissected or the therapeutic ratio, especially in the era of neoadjuvant therapy, template dissection should be attempted [39]. Types of lymphadenectomy are presented in Table 2.

Three field lymphadenectomy (3F) showed improvement in survival without significant increase in complications or mortality in earlier studies [40, 41]. However, most reported studies had small numbers or historical controls. A meta-analysis in 2014 (2 RCT and retrospective studies) demonstrated increased rate of complications (recurrent nerve palsy and anastomotic leakage) with 3F when compared to two field (2F) dissection but improved overall survival [42]. The confounding factor of stage

Table 2 Types of lymphadenectomy

Type of lymphadenectomy	Nodal fields resected
Standard two-field lymphadenectomy	Abdominal field + infracarinal thoracic field
Extended two-field lymphadenectomy	Right superior mediastinal clearance + standard two-field
Total mediastinal lymphadenectomy	Bilateral supracarinal clearance + standard two-field
Three-field lymphadenectomy	Abdominal field + total mediastinal field + cervical field

migration due to extensive lymph node dissection could have shown apparent improvement in survival. In the east (Japan), 3F lymphadenectomy is routinely practiced with all esophagectomies; however due to lack of conclusive evidence and a recent RCT demonstrating no significant improval in survival with 3F over 2F lymphadenectomy [43], it is not recommended in the management guidelines of the west. The advantage of 3F over conventional 2F remains speculative and could be answered by ongoing randomized trials [44, 45].

7.5 Surgical Reconstruction

The stomach is the preferred conduit for reconstruction due to its good vascular supply and single anastomosis to restore continuity. Colon or jejunum are the other alternate options. Pyloric drainage procedure in case of stomach conduit has shown to decrease aspiration and hence pulmonary complications [46].

Route of reconstruction—The posterior mediastinum or the retrosternal route are the two options and both have shown similar perioperative outcomes and conduit function [47].

Anastomosis—Stapled or handsewn (end to end) anastomosis in the neck or intrathoracic location have shown similar leak rates but the stricture rate is high with circular staplers [48].

7.6 Neoadjuvant Therapy

Locally advanced esophageal cancers (T3–4/N0 and T1–4/N+) are treated with neoadjuvant therapy followed by surgery as part of multimodal approach. Neoadjuvant treatment with chemotherapy (NACT) or chemoradiotherapy (NACRT) have been evaluated in multiple studies. Neoadjuvant radiotherapy (NART) alone, has not been shown to be beneficial.

- *Preoperative chemoradiation*—Meta analyses comparing NACRT with surgery to surgery alone has reported improved 3 year survival and reduced locoregional recurrence [49, 50]. However, there was increased morbidity and mortality associated with combined treatment. The randomized CROSS trial and NEOCRTEC trial comparing NACRT followed by surgery to surgery alone showed significantly improved survival (49.4 versus 24 months), 92% R0 resection rate and improved pathological response in the neoadjuvant group, while the postoperative complication profile was similar in both groups. The CROSS protocol constituted radiation of 41.4 Gy/23 fractions over 5 weeks with concurrent weekly chemotherapy (paclitaxel 50 mg/m^2 and carboplatin at area under the curve of 2 mg/mL/min) [51]. The long-term results of the CROSS trial confirmed the overall survival advantage of NACRT in all subgroups and also improved local and distant recurrence rates [52].
- *Preoperative chemotherapy*—Multiple meta-analyses of NACT trials have shown that preoperative chemotherapy followed by surgery appears to offer an absolute 2 year survival advantage ranging from 4% to 11% for both adenocarcinoma and SCC, when compared with surgery alone for resectable esophageal cancer [53]. Chemotherapy regimens commonly used are 5FU/Cisplatin and ECF (Epirubicin, 5FU and Cisplatin) [54]. The Medical Research Council (MRC) trial of 802 patients demonstrated that two cycles of cisplatin and 5-fluorouracil in the neoadjuvant setting improved survival without additional adverse events [55]. Perioperative chemotherapy was evaluated in the MAGIC trial (ECF regimen) [54] and more recently the FLOT 4 study (DOF regimen) [56] in gastric and GEJ adenocarcinoma. Both the trials have shown significantly better overall survival as well as progression-free survival.
- A meta-analysis evaluated NACRT and NACT in esophageal carcinoma, and found strong evidence for absolute survival benefit with both forms of neoadjuvant therapy over surgery alone; however there was no clear advantage of NACRT over NACT [57].

7.7 Adjuvant Therapy

Few studies in patients with esophageal cancer treated with primary surgery have evaluated the role of adjuvant therapy; theoretically, this benefit is likely to be highest in patients with metastatic nodal disease or margin positivity on histopathology. So far, none of these studies have shown a clear survival benefit.

- *Postoperative radiotherapy*—Currently, the only indication of adjuvant radiation is positive margins or residual disease. Adjuvant radiation without chemotherapy has not shown benefit consistently in clinical trials.
- *Postoperative chemotherapy*—Adjuvant chemotherapy is beneficial in patients with nodal disease in adenocarcinoma of the esophagus. Perioperative (three cycles pre and three cycles postoperative) chemotherapy for lower esophageal and GE junction cancers, has been shown to be beneficial as trials have demonstrated both disease-free and overall survival advantage [54, 55]. However, a phase III study by Japanese Clinical Oncology Group (JCOG) reported no difference in overall survival and only a small benefit in disease-free survival [58]. Postoperative adjuvant nivolumab for patients with resid-

ual pathological disease after neoadjuvant chemoradiation followed by surgery in esophageal SCC has shown significantly better disease free survival (CheckMate577 trial) and has been recommended in the latest NCCN guidelines.

- *Postoperative chemoradiotherapy*—Adjuvant chemoradiotherapy may be considered in patients who have not received neoadjuvant treatment with lower third and GEJ adenocarcinoma patients based on results from the Intergroup INT0116 trial [59].

7.8 Definitive Radiation/Chemoradiation

The nonsurgical curative option, evaluated for unresectable esophageal cancers and medically inoperable patients, is definitive chemoradiation. It is also the treatment of choice for upper third esophageal cancers. Earlier studies looked at radiotherapy alone as primary treatment, but were found to have poor outcomes and high local failure rates. Following this, combined modality of concurrent chemoradiation (50 Gy with Cisplatin/5FU) was tested in RTOG 85–01 trial, which reported better overall survival when compared to 64 Gy radiotherapy alone [60]. These results were similar for both SCC and adenocarcinoma and it formed the precedent for accepting definitive chemoradiation as a curative treatment option for locally advanced unresectable esophageal cancers. However, as the local failure rates remained high, dose escalation was evaluated in Intergroup (INT-0123) trial, where increasing the dose of radiation from 50.4 Gy to 64.8 Gy in concomitant chemo radiotherapy setting did not result in improved survival [61]. The most commonly used regimen is 60–64 Gy/30–32 fractions over 4–5 weeks with conventional fractionation and 4 cycles of cisplatin (75–100 mg/m^2 on day 1) and 5-fluorouracil (750–1000 mg/m^2/day × 4 days). A margin of 5 cm above and below the primary tumor with a radial margin of 1–1.5 cm is recommended to account for subclinical disease spread and periesophageal nodes.

Intensity-modulated radiation therapy (IMRT) is a modern technique which can be used to deliver higher doses of radiation, protecting the surrounding vital organs like the heart and lung and thereby having more tolerable adverse effects. A retrospective analysis has shown reduced toxicity profile with IMRT and improved survival [62].

Another method to escalate radiation dose is intraluminal brachytherapy (ILRT) which is used as a boost to external beam radiation (EBRT). A brachytherapy catheter with a diameter of 6 to 10 mm is placed endoscopically in the esophageal lumen and a dose of 5–10 Gy per fraction in 1 to 4 fractions is delivered in addition to 50 Gy EBRT [63]. Treatment related fistulas are a common adverse effect; hence, patients need to be selected appropriately.

7.9 Palliative Treatment

Patients with advanced, metastatic esophageal cancer need to be managed with the goal of prolonging survival and maximizing their quality of life. Pain and dysphagia are two most common symptoms to palliate. Pain may be managed with narcotics (both short acting and long acting) and local radiotherapy in case of bone metastases. Palliation options for dysphagia include (1) Esophageal self-expanding metallic stent; (2) EBRT; (3) ILRT; (4) Feeding tubes; or a combination of these methods.

- Palliative radiotherapy.
- Palliative radiation with 30–35 Gy over 10–15 fractions, has been shown to improve dysphagia in 70% to 90% of patients [64]. ILRT is another effective method to palliate dysphagia. A Dutch study comparing esophageal stents and 12 Gy ILRT showed that there was rapid improvement in dysphagia with stent placement; however, long-term relief was better with ILRT [65]. The onset of dysphagia improvement with radiation is slow and takes around 2 weeks, but is more long-lasting when compared with other modalities.

- Palliative chemotherapy.

- Multiple regimens have been used in advanced esophageal cancer patients with preserved general condition. Dysphagia relief with chemotherapy is modest. Some studies show prolongation of survival with palliative chemotherapy when compared to best supportive care [66]. Trastuzumab, as targeted therapy, along with chemotherapy may be considered in Her-2 positive metastatic gastroesophageal cancer patients.
- In case of tracheoesophageal fistula, if the tracheal lumen is compromised, tracheal/bronchial stent may be placed. A retrospective review looking at airway involvement in esophageal cancers showed that induction chemotherapy followed by radical intent radiation was feasible in 80% of patients and there was modest improvement in survival [67].
- In patients with poor general condition:

    - Nutritional rehabilitation with nasogastric tube placement.
    - Supportive care.

7.10 Management of Recurrent Disease

- Salvage surgery for localized recurrence.
- Locoregional chemoradiotherapy for localized failures postsurgery.
- Palliative treatment or supportive care.

Table 3 Stage-wise management

Stage	Management
Stage 0 esophageal cancer	Endoscopic resection
	Surgery
Early disease—T1 or T2, N0	Surgery alone
T3 or T4, N0 Any T, N+	Chemoradiation followed by surgery
	Chemotherapy followed by surgery
	Definitive chemoradiation
Any T, any N, M1	Palliative radiotherapy
	Palliative chemotherapy
	Endoscopic-placed stents to provide palliation of dysphagia
	Nd:YAG endoluminal tumor destruction or electrocoagulation
Recurrent esophageal cancer	Salvage with either surgery or chemoradiation in localized treatment failures
	Palliative use of any of the standard therapies, including supportive care

Table 3 presents stage-wise management of esophageal cancer.

8 Summary: How We Do It at TMC

As a tertiary referral center, Tata Memorial Centre, Mumbai, registers around 1200–1300 patients with esophageal cancer annually. They are initially evaluated with upper GI endoscopy to confirm diagnosis and PET-CT for staging when radical intent treatment is planned. Nutritional and pulmonary rehabilitation is started simultaneously. Upper- and middle-third tumors undergo bronchoscopic evaluation.

- Upper-third cervical esophageal cancers: Definitive chemoradiation is the treatment of choice.
- Mid- and lower-third esophageal cancers:
  - Early low volume esophageal disease needs additional EUS for accurate staging. A small proportion of the early lesions (select T1a) undergo endoscopic treatment (EMR/ESD), while most of them (T1, T2 N0) are treated with upfront surgery.
  - Locally advanced operable disease needs additional staging laparoscopy for GEJ adenocarcinoma. Neoadjuvant therapy (NACT or NACRT) followed by surgery is the standard of care for operable cancers. Perioperative chemotherapy (FLOT-4 or ECF regimens) for adenocarcinoma and NACT or NACRT for SCC is administered. CECT thorax is used for response assessment post induction therapy. The preferred surgical approach is TTE with standard two field lymphadenectomy. We perform a radical three field lymphadenectomy for patients with supracarinal nodal disease or as part of a randomized trial. For patients with compromised lung function or high-risk comorbid disease, THE is considered a suitable option and GEJ tumors are approached with LTA incision. Minimally invasive approach is employed in around 30% of patients. The preferred conduit is the stomach through the posterior mediastinal route. We prefer a linear stapled anastomosis and insert a nasojejunal tube for feeding in the immediate postoperative period.
  - Locally advanced inoperable disease is treated with definitive chemoradiation.
  - Metastatic disease patients are managed with either palliative radiotherapy or best supportive care for SCC and palliative chemotherapy for adenocarcinoma.

Esophageal cancer continues to carry dismal prognosis in spite of advances in treatment modalities with 5-year survival varying between 5% and 30%. Multidisciplinary team management is the way forward to try and improve survival in esophageal cancer patients.

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Biliary Tract Cancer

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Abbreviations

APBDJ	Anomalous pancreaticobiliary duct junction
BD	Biliary drainage
CCA	Cholangiocarcinoma
CEA	Carcinoembryonic antigen
CEUS	Contrast-enhanced ultrasonography
CT	Computed tomography
CTRT	Adjuvant chemoradiotherapy
dVSS	Da Vinci robotic surgical system
EBRT	External beam radiotherapy
ESMO	European Society of Medical Oncology
EUS	Endoscopic ultrasonography
GBC	Gallbladder cancer
HR	Hazard ratio
IORT	Intra-operative radiotherapy
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NACT	Neoadjuvant chemotherapy
PET	Positron emission tomography
SEER	Surveillance, epidemiology, and end result
TNM	Tumor-node-metastasis
USG	Ultrasonography

1 Gallbladder Cancer

1.1 Introduction

Gallbladder carcinoma (GBC) is the fifth most common gastrointestinal tract malignancy [1] with considerable geographical and ethnic variation in the incidence. Worldwide the highest incidences of GBC are reported in South American countries like Chile (16–27/100,000), Ecuador, and Bolivia, and in India, south Pakistan, and Central Europe [2]. Worldwide, the age-standardized incidence rate is 2.2 for males and 2.4 for females, while the mortality rate is 1.6 and 1.8, respectively [3]. The lifetime risk of developing GBC is 0.25 for males and 0.26 for females.

GBC has a distinct demographic divide in India with the highest prevalence in the northern states of Uttar Pradesh, Bihar, Orissa, West Bengal, and Assam [4, 5] and is the leading gastrointestinal tract cancer in women residing in north Indian cities [6]. According to Tata memorial hospital registry, it is the fourth most common malignancy in females [7]. The incidence of GBC increases after the age of 45 years and is maximum at the age of 65 years [8].

The overall 5-year survival for GBC is only 20%. Five-year overall survival for various stages is stage I, 62.5%; II, 50.2%; IIIA, 25.7%; IIIB, 22.1%; IVA, 15.7%; IVB, 6.7%.

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1.2 Etiology and Risk Factors

1.2.1 Age and Gender

GBC rates increase with increasing age with a median age in the sixth decade of life. Increasing age also corresponds to an increase in mortality [2].

GBC is twice more common in women than men and is correlated with increased parity and a greater number of pregnancies [2, 9]. Marked female predominance is seen especially in northern India, Pakistan, and the American Indian population.

1.2.2 Geography and Ethnicity

There is a wide difference in the geographical pattern for GBC with very high incidence in Asia and South America, with Asia being the high-risk continent [2]. The highest incidence is seen in north Indian and Pakistani women and Korean men. GBC is also common in indigenous populations of Makuchi Indians and American Indians [9, 10]. The incidence is relatively low in most Western and Mediterranean European countries.

1.2.3 Gallstones

There is no direct causal relationship between gallstones and GBC, although 75–98% of all GBC patients have associated cholelithiasis. However, the incidence of GBC gallbladder cancer in a population of patients with gallstones is only 0.3–3% [9]. Gallstones carry a relative risk of 4.9 for GBC [2]. Stones larger than 3 cm and cholesterol gallstones carry an increased risk [9]. Risk factors predicting incidental gallbladder cancer following cholecystectomy include older age, female sex, previous cholecystitis, and the combination of acute cholecystitis without jaundice and jaundice without acute cholecystitis [11, 12].

1.2.4 Chronic Inflammation

Chronic inflammation is a major risk factor for GBC. Gallstones resulting in chronic cholecystitis are a well-recognized risk factor. Chronic inflammation leads to changes in cell proliferation, cell death (apoptosis), DNA mutation rates, DNA methylation, and angiogenesis [9].

1.2.5 Porcelain Gallbladder

Chronic inflammation also results in calcium deposition in the gallbladder wall. Such depositions are more common in elderly women in the sixth decade. Gallbladders with extensive calcifications particularly of stippled or punctate type are considered premalignant with 21% harboring malignancy [13].

1.2.6 Infections

Chronic bacterial infections due to S. typhi/paratyphi and H. bilis are associated with an increased risk for GBC [9].

Malignant transformation is implicated via the degradation of bile constituents and chronic inflammation itself. A chronic carrier state is associated with an increased risk of GBC with an OR of 4.13, and the association is more prominent in patients without gallstones [14, 15].

1.2.7 Primary Sclerosing Cholangitis

Gallbladder lesions are found in 6% of patients with sclerosing cholangitis with >50% of them harboring malignancy. Increased risk is related to chronic inflammation leading to metaplasia-dysplasia-carcinoma sequence. Cholecystectomy is performed even in polyps <1 cm associated with this disease due to the higher risk of GBC [16].

1.2.8 Obesity

Obesity (BMI >30 kg/m^2) clearly predisposes to GBC. The pooled relative risk for GBC for overweight and obesity is 1.1 and 1.58, respectively, and the risk increases by 4% for each 1 kg/m^2 increment in BMI. The risk is higher in obese females (RR of 1.68) than in males [17].

1.2.9 Gallbladder Polyps

Gallbladder polyps have a prevalence of 0.3–9.5% in the general population with 70% of them being pseudopolyps (cholesterol, focal adenomyomas, inflammatory) which do not carry malignant potential. High-risk features in polyps include large polyps (>1 cm; one-quarter being malignant); a solitary polyp; a sessile polyp; polyp growth; associated gallstones; age over 50–60 years and Indian ethnicity. Cholecystectomy is recommended in the presence of these risk factors [18].

1.2.10 Anomalous Pancreaticobiliary Duct Junction (APBDJ)

APBDJ is a congenital anomaly commonly identified in Asian individuals, particularly of Japanese origin. The carcinogenesis is related to the hyperplasia-dysplasia-carcinoma sequence as a result of the reflux of pancreatic juices into the biliary tract and associated chronic inflammation. Biliary tract cancer is detected in 21.6% of adult patients with congenital biliary dilatation and in 42.4% of adult patients without biliary dilatation with GBC being the most common malignancy [19, 20].

1.2.11 Genetics

Family history is a significant risk factor for GBC. Genetic alterations in oncogenes, tumor suppressor genes, and microsatellite instability predispose to GBC. Proposed carcinogenic pathways include 1) gallstone-mediated inflammation 2) K-ras point mutations (as observed in patients with an anomalous junction of the pancreaticobiliary duct) and 3) neoplastic foci in gallbladder polyps [21].

Genome-wide association study from India has identified a strong association between common genetic variants in the ABCB1 and ABCB4 genes and the risk of gallbladder cancer along with phospholipase C epsilon 1(PLCE1) and liver X receptor beta (LXR) interactions [21, 22].

1.3 Clinical Features

The presentation of GBC is generally nonspecific. Most patients present at an advanced stage with anorexia, jaundice, pruritis, and a lump in the right hypochondrium along with poor performance status.

There is also a possibility of detecting GBC on imaging done for unrelated symptoms. "Incidental GBC" is termed when GBC comes as a surprise finding upon histopathological examination of the cholecystectomy specimen, without suspicion on pre-operative imaging or on intra-operative findings.

1.4 Diagnosis and Work-Up

1.4.1 Blood Investigations

Derangement of liver function tests is a sign of advanced disease. Tumor markers—carcino-embryonic antigen (CEA) and carbohydrate antigen (CA 19–9) are uncertain for diagnosis as these are not specific for GBC. A CEA >4 mg/mL and CA 19–9 with a cut-off value of >20 IU/mL have a sensitivity of 50% and 79% and specificity of 93% and 79% respectively [14, 23].

1.4.2 Imaging

Ultrasonography (USG)

Findings that are suspicious of GBC are the presence of asymmetric wall thickening or calcification, and gallbladder mass with loss of a fat plane between the gallbladder and liver. Gallbladder polyps over 1 cm in diameter are highly suspicious. Other useful USG findings are enlarged nodes, infiltration into surrounding organs, liver metastasis, and biliary dilatation, [24]. The sensitivity of USG in the advanced stage is 84.6% and global accuracy is 90.5% [25]. However, for early lesions diagnostic accuracy is less.

Contrast-Enhanced Ultrasonography (CEUS)

Contrast-enhanced ultrasound using microbubbles as a contrast agent has shown promising results to differentiate malignant lesions in the gallbladder. The sensitivity and specificity for differentiating these lesions on CEUS are 0.81 and 0.87 respectively. Features suggestive of malignancy include discontinuity of the gallbladder wall, infiltration to the surrounding tissue during enhancement, tortuous intralesional vessels, and thickened gallbladder wall [26].

Computed Tomography (CT) Scan

Contrast-enhanced CT is the best modality to define the loco-regional extent of disease as well as distant metastasis (Fig. 1). On a CT scan, GBC usually appears as a mass or a focal or diffuse thickening of the gallbladder wall. Tumor mass is usually heterogeneous with non-uniform uptake of contrast. A CT scan helps stage the disease more accurately by depicting invasion into adjacent liver parenchyma or bile duct and metastases to the liver, periportal and retroperitoneal nodes, and peritoneum. The sensitivity of CT is 0.36 to 0.47 for N-staging (PPV: 0.94; NPV: 0.92); 0.65 for hepatic infiltration of <2 cm (PPV: 0.77) and 1.0 for >2 cm (PPV: 1.0) [27].

Magnetic Resonance Imaging (MRI) and Magnetic Resonance Cholangiopancreatography (MRCP)

MRI and MRCP (Fig. 2) are of particular value in patients presenting with obstructive jaundice. They help in detecting accurately the extent of the bile duct and vascular involvement.

Endoscopic Ultrasonography (EUS)

EUS has an overall accuracy of 80% to detect gallbladder anomalies [26]. Other advantages include assessment of depth of invasion, vascular invasion, periportal lymphadenopathy, and allowing FNAC from suspicious areas/lymph nodes.

[18F]-2-Deoxy-D-Glucose (FDG) Positron Emission Tomography (PET)

In patients with GBC, 18-FDG positron emission tomography (PET)-CT detects occult peritoneal, omental, and/or lymph node metastases with a sensitivity of 56% (Fig. 3)

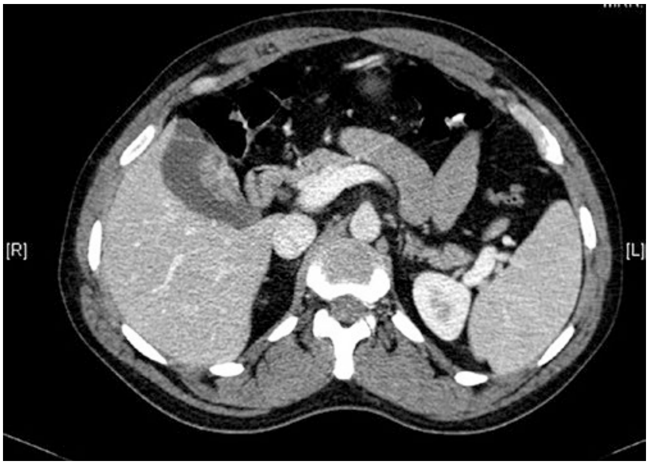


Fig. 1 Early gallbladder cancer

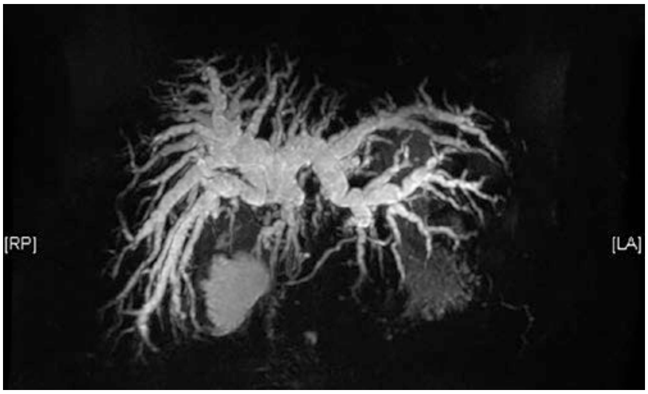


Fig. 2 MRCP showing type I block

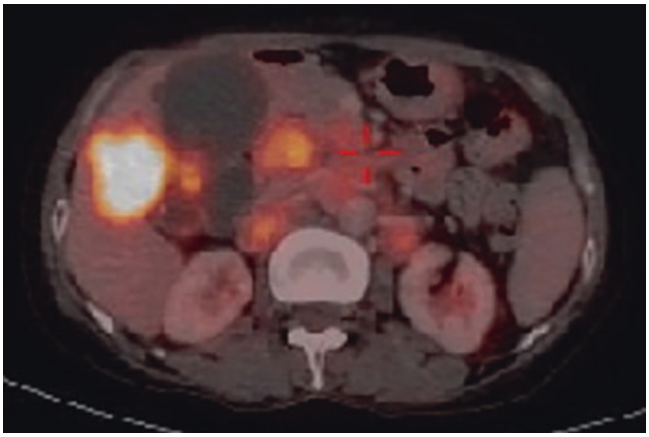


Fig. 3 PET CT showing retroperitoneal nodes

[18]. There is an emerging role of FDG PET scans in incidental GBC with 78% sensitivity and 80% specificity in detecting residual disease [28, 29]. FDG PET CT scans should be done at least 4–6 weeks after any surgical intervention to avoid false positives.

1.4.3 Biopsy and Cytology

A biopsy is not indicated in resectable GBC to avoid seeding of the peritoneum, biopsy tracts, and surgical wounds [30]. Percutaneous FNAC and core needle biopsy should be performed for unresectable or metastatic lesions not considered for upfront surgical resection. Percutaneous biopsy has an accuracy rate of above 90% with a negligible false positive rate. Sensitivity for bile cytology is approximately 75% and is unwarranted in resectable patients.

1.4.4 Staging Laparoscopy

Staging laparoscopy should be done in all patients with resectable advanced GBC or incidental GBC before proceeding to radical surgery to rule out distant and peritoneal metastases. It can prevent a non-therapeutic laparotomy in 38–62% of patients and help in the detection of N2 disease [31]. The yield is highest for patients with T3 disease, poor differentiation, or positive cystic duct margin status [32].

1.5 Staging

Multiple staging systems have been proposed in the past for GBC staging—the American Joint Committee on Cancer (AJCC), the Japanese Biliary Surgical Society system, the Nevin system, and the modified Nevin systems. The AJCC TNM staging (eighth edition) of gallbladder cancer is the standard reporting mechanism [33]. For the eighth edition, the T2 category is separated into T2a (stage IIA) and T2b (stage IIB), based on tumor location on the peritoneal or hepatic side of the gallbladder, respectively. This change is based on a multicenter study demonstrating worse survival for tumors on the hepatic side of the gallbladder [34]. Also, N1 is now defined as one to three metastatic lymph nodes, and N2 as four or more metastatic lymph nodes for better prognostic stratification [35].

1.5.1 Pathological Evaluation of Routine Cholecystectomy Specimens

A step-wise sampling protocol should be followed to identify early dysplastic lesions [36, 37]. In areas of high GBC prevalence even with normal gross examination, a minimum of three random areas and the cystic duct margin should be submitted for microscopic assessment. A thorough sampling is also necessary in the presence of high-risk features like a choledochal cyst, APBDJ, sclerosing cholangitis, and hyalinizing cholecystitis/porcelain gallbladder.

1.5.2 Treatment

Surgery

Surgery is the definitive treatment for non-metastatic GBC (Fig. 4). The standard surgery for GBC includes en-bloc removal of the gallbladder with wedge excision of the liver (2.5–3 cm liver wedge/segment IV b and V) or anatomical segment IVB/V excision along with radical periportal lymphadenectomy and a frozen section for negative cystic duct margin.

The Extent of Liver Resection

The goal is to obtain R0 resection with negative margins. The size of the wedge liver resection depends on the depth of the tumor infiltration and bile duct involvement, ranging from limited segment IVB and V wedge resections to formal anatomic resections [38].

There is no survival advantage of major hepatectomy or formal segment IVb/V resection compared with non-anatomic R0 resection of the liver wedge/gallbladder bed [39–41].

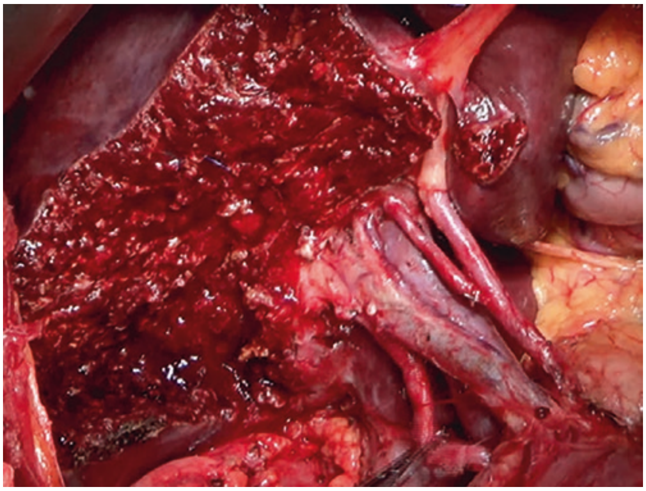


Fig. 4 Complete periportal lymphadenectomy with liver wedge resection

Lymph Node Dissection

Lymph node involvement varies by T-stage, approximating 12%, 31%, and 45% in patients with T1b, T2, and T3 tumors, respectively [40]. The presence of N1 nodal disease is not considered an absolute contraindication to surgical resection. Removal of at least six lymph nodes is recommended for accurate staging [42].

Inter-aortocaval nodal (Station 16) sampling forms the first step of lymphadenectomy. The presence of a positive station 16 lymph node indicates non-regional lymph nodal metastasis [43]. The highest peri-pancreatic lymph node is the transition between the N1 and N2 fields with a good prognostic value. A standard portal lymphadenectomy for GBC includes nodes in the porta hepatis, gastrohepatic ligament, and retroduodenal space (Station 8,12,13).

Bile Duct Resection

Routine bile duct resection has no role in GBC surgery and is not associated with higher lymph node yield [44]. Radical cholecystectomy with extrahepatic bile duct resection should be performed for patients with positive cystic duct margin or if there is a need to achieve nodal clearance for bulky nodal disease involving hepatoduodenal ligament, with GBC involving the neck and cystic duct with direct infiltration of bile duct [45]. Routine bile duct resection should be avoided to prevent additional morbidity.

Role of Multi-Visceral Resection—Major Hepatectomy and Hepatopancreaticoduodenectomy

In the absence of outcome data, associated morbidities, and inherent aggressive tumor biology, these resections are not routinely performed and are not recommended. However smaller series have reported good outcomes in carefully selected patients [46].

A major hepatectomy may be considered in the absence of hepatic arterial involvement or liver metastases [47]. Hepatopancreaticoduodenectomy is associated with a postoperative morbidity rate of 78.9% and a mortality rate of 10.3% with postoperative hepatic failure being the most common reason for mortality [48]. However, it can provide a rare chance of long-term survival in patients in whom R0 curative resection is feasible.

Role of Minimal Invasive Surgery

Radical cholecystectomy with a minimally invasive approach is rarely reported due to the perceived risk of gallbladder perforation and peritoneal dissemination [49, 50]. Two systematic reviews for a minimally invasive approach concluded that it cannot be considered as a dogmatic contraindication for GBC and when performed at a highly specialized center is safe and feasible [51].

The da Vinci robotic surgical system (dVSS) with its improved dexterity, surgeon-controlled camera, and 3D vision has resolved many technical problems associated with a conventional laparoscopic approach and has shown equivalent perioperative and short-term oncological results as compared to open radical cholecystectomy [52, 53].

Early GBC (pTis and pT1a)

Early GBC is suspected preoperatively in only 30–40% on imaging with most of them discovered incidentally on histopathological examination of cholecystectomy specimens performed for other reasons.

The optimum treatment for pTis and pT1a GBC is simple cholecystectomy with a negative cystic duct margin with a cure rate of 85–100% [54]. However, the presence of perineural or vascular invasion on histopathology or bile spill during cholecystectomy may adversely affect long-term survival [55].

pT1b GBC

The incidence of nodal metastases with T1b disease is 3.8–25% [56]. Radical cholecystectomy for T1b disease includes cholecystectomy with en-bloc hepatic bed resection (2–3 cm wedge resection or segment IVb + V) and peri-portal lymphadenectomy with or without bile duct excision for negative margin [57].

pT2 GBC

T2 disease has lymph node metastasis in 20–62%, mainly to hepatoduodenal ligament and location of the tumor on the hepatic side, i.e., pT2b carries poor prognosis due to higher rates of nodal positivity and vascular invasion [58]. In these patients, radical cholecystectomy is the treatment of choice. SEER database has shown a survival benefit with extended surgical resection and lymph node dissection with pT2 GBC [59]. In a study by Matsumoto et al., 3 years of survival of

Stage II GBC treated with simple vs. radical cholecystectomy was 57% vs. 100% [60].

Incidental GBC

The incidence of incidental GBC is 0.35–2% [61]. Incidental GBC gallbladder cancer has a better prognosis compared to non-incidental disease if managed appropriately with R0 resection. The incidence of residual disease is as high as 37.5% in T1 tumors, 56.7% in T2 tumors, and 77.3% in T3 tumors [62].

On suspicion of GBC during laparoscopic surgery, the procedure should be aborted and the patient referred to a specialized hepatobiliary center. A review of pre-cholecystectomy imaging and a discussion with referring surgeon regarding intra-operative findings should be done. Both CT scans and MRIs provide critical information in re-staging the patients. There is now an increasing role of PET scans in restaging disease in incidental GBC. The management of incidental GBC is guided by the TNM stage. Radical re-resection or revision surgery is advocated in patients with pT1b and above GBC. Delaying resection has no effect on the outcome of the disease. There is no significant impact on the time interval between cholecystectomy and radical re-resection [63]. Revision surgery should be performed whenever feasible.

Port Site Resection

Port site resection was advocated in the past to reduce the local wound recurrence due to the possibility of tumor contamination at the time of laparoscopic cholecystectomy. Recent evidence suggests port site metastases as a harbinger of generalized peritoneal recurrence that would not be prevented with resection of these sites. Port site resection is not associated with improved overall survival or recurrence-free survival [64] and is no longer considered as part of standard surgery for GBC.

Locally Advanced GBC (T3, T4, and Node-Positive) and Role of Neoadjuvant Treatment

T3 disease has a higher incidence of residual disease-36% and metastatic nodes-46%. Management includes radical resection of the gallbladder fossa with portal lymphadenectomy and a negative cystic duct margin. In the case of T4 disease, the role of extensive vascular reconstructions in the treatment of gallbladder cancer has not been shown to provide a survival benefit. All such patients can be termed as 'high risk' GBC and may be offered neoadjuvant treatment.

Role of Neoadjuvant Chemotherapy (NACT)

The neoadjuvant approach to GBC has emerged as a bridge to possible surgery as well as an assessment of disease biology based on the assessment of response to NACT or CRT. Engineer et al.'s study of 28 patients with T3/T4 disease with fixed portal nodes used CRT with gemcitabine and achieved an R0 resection rate of 56% and mOS of 20 months [65].

Considering the systemic nature of GBC as well as a predominantly distant recurrence pattern as opposed to locoregional recurrences, the use of NACT with lesser morbidity is likely to be the treatment of choice. The use of a gemcitabine-platinum combination (either cisplatin or oxaliplatin), based on the regimen's efficacy has been explored in two retrospective studies from the Tata Memorial Hospital and MSKCC, respectively. R0 resection rates were 46% and 14%, respectively, though mOS was similar in both cohorts (13.4 months and 14 months respectively) [66, 67]. Chaudhari et al. in their study evaluating the role of NACT, defined the criteria for high-risk disease (TMH criteria- based on clinic-radiological parameters). These criteria can be used in the future to select patients for NACT in GBC [68].

A randomized study comparing chemotherapy alone with CRT in locally advanced GBC satisfying pre-defined criteria is currently recruiting in Tata Memorial Hospital and may provide answers post-completion [69].

1.6 Adjuvant Therapy

Studies on adjuvant treatment in GBC are retrospective in nature. External beam radiotherapy (EBRT), intra-operative radiotherapy (IORT), and brachytherapy with or without chemotherapy have been used in the past for adjuvant treatment of GBC [69–75].

Currently, adjuvant therapy is recommended in all patients with stage II to IVA GBC patients who have undergone radical cholecystectomy. Patients who have tumor confined to lamina propria that is diagnosed incidentally do not need adjuvant treatment as their survival approaches 100% with simple cholecystectomy alone [76].

1.6.1 Adjuvant Chemotherapy

A phase III RCT from Japan by Takada et al. [77] evaluated the role of adjuvant chemotherapy in pancreatobiliary cancers. The 5-year OS and disease-free survival rate in GBC patients was significantly better in the chemotherapy group (26.0%, 20.3%) compared with the control group (14.4%, 11.6%) ($p = 0.0367$, $p = 0.0210$). However, statistically significant survival benefit was observed in patients who underwent non-curative resection (8.9% vs. 0%; $p = 0.0226$) but not in patients with completely resected GBC.

The lack of adequate randomized phase III data suggesting a definitive benefit to adjuvant therapy has hampered the uptake of this modality in biliary tract cancers (BTC) till recently. However, multiple retrospective studies, single-arm studies, and meta-analyses have suggested that improved outcomes post resected BTC have been a combination of standardized surgical techniques as well as adjuvant therapy.

The majority of available evidence for the role of adjuvant therapy in resected BTC has been crystallized in three well-conducted meta-analyses [78–80]. These studies primarily comprise retrospective and single-institution studies (which is indicative of the lack of randomized data in these tumors) as well as a mix of CC and GBC, the following suggestions for adjuvant therapy are to be considered:

1. There appears to be no major difference in terms of outcomes between CC and GBC when adjuvant therapy is received.
2. The strongest evidence for the benefit of adjuvant therapy is in the presence of lymph node-positive disease and R+ resections.
3. Adjuvant chemotherapy and adjuvant CRT are potentially superior to adjuvant radiotherapy alone, though there is no available data or consensus as to the primacy of chemotherapy over CRT or vice-versa.
4. There is no available data to suggest the adjuvant chemotherapy regimen of choice. Guidelines suggest the use of regimens that are effective in advanced unresectable BTC (e.g., gemcitabine-cisplatin, gemcitabine-oxaliplatin).

The PRODIGE 12-ACCORD 18 (UNICANCER GI) study and the BILCAP studies are two randomized studies in the current era which have further defined the role of adjuvant chemotherapy in resected BTC [81, 82]. While the PRODIGE-ACCORD trial used the gemcitabine-oxaliplatin regimen versus observation as an adjuvant, BILCAP randomized patients to single-agent capecitabine or observation. The PRODIGE-ACCORD trial did not reach its primary endpoint of superior recurrence-free survival (RFS) [30.4 months for gemcitabine-oxaliplatin vs. 22 months for observation, p = 0.31; HR - 0.83 (95% CI: 0.58–1.19], the BILCAP study reached its primary endpoint of statistically superior mOS (53 months for capecitabine vs. 36 months for observation, HR 0.75 [95%CI 0.58, 0.97; p = 0.028]) on per-protocol analysis. While the BILCAP study does suggest that single-agent capecitabine may be considered as one of the current standards of care, certain caveats do exist. The study considered BTC as a whole, whereas it is well known that GBC and CC have different molecular characteristics and behavior. Secondly, the lack of patients in these studies from high-endemic regions of BTC (Chile, India, Thailand, etc.) may hamper the generalization of this data across regions.

1.6.2 Adjuvant Chemoradiotherapy (CTRT)

The evidence for the use of adjuvant (chemo) radiation for patients with resected gallbladder cancer is supported by Surveillance, Epidemiology and End Result (SEER) database that included 1137 patients. While the SEER database analysis support use of adjuvant chemoradiation in stage >pT2, pN+ patients the absolute benefit in an individual patient may be estimated using proposed nomograms [83]. A dose of 45 Gy in 25 fractions over 5 weeks may be acceptable and has been shown to improve outcomes in patients with GBC. A boost of 5.4 Gy may be considered in an R1 resection. The limiting feature of local irradiation is the tolerance of surrounding critical structures, including the liver, kidneys, pancreas, lesser curvature of the stomach, and small bowel.

Another analysis of the National Cancer Database that included 5029 patients reported improved survival in all patient categories apart from T1N0 and is also supported by multi-institutional analysis [84, 85]. However, despite this evidence, the utilization of adjuvant chemotherapy or chemoradiation is low, and prospective randomized trials should be done to confirm the efficacy of adjuvant chemoradiation over adjuvant chemotherapy in high-risk resected gallbladder cancer.

1.7 Management of Unresectable/ Metastatic GBC

The current standard of care for patients with unresectable BTC with good performance status and adequate organ function is palliative chemotherapy with concurrent early palliative care. The benefit of palliative chemotherapy over best supportive care (in terms of quality of life and prolongation of life) was proven with a small randomized study as early as 1996 [86]. Since then, various chemotherapeutic regimens, predominantly combining 5-fluorouracil, capecitabine, gemcitabine, and either of the platinum have been used in various combinations to improve survival. The ABC-02 and BT-22 studies established gemcitabine-cisplatin as the current standard of care when compared to single-agent gemcitabine alone [87, 88]. The gemcitabine—oxaliplatin combination is also commonly used with a study from AIIMS having shown its superiority of 5—fluorouracil and best supportive care [89]. Available evidence suggests that both platinum-based doublets have similar efficacy and outcomes. The combination of gemcitabine and S1 (an oral drug combining tegafur, gimeracil, and oteracil potassium) has also shown non-inferiority to gemcitabine-cisplatin as per the results of the Japanese JCOG1113- FUGA-BT study [90].

The use of monoclonal antibodies (e.g., bevacizumab) and anti-EGFR tyrosine—kinase inhibitors (e.g., cetuximab, Panitumumab, etc.) in unresectable BTC has not shown significant benefit and the use of such drugs is not currently recommended outside the setting of a clinical trial.

The role of chemotherapy as opposed to active symptom control post progression on first-line chemotherapy is an unanswered question, though studies like the ABC-06 may provide answers in the future.

1.8 Palliative Care

Patients with advanced disease often experience severe upper abdominal pain which should be treated in a stepwise manner with escalating doses of non-opioid and opioid drugs and celiac plexus block under imaging in unrelenting cases.

Biliary obstruction leading to jaundice and pruritus should be relieved by biliary stenting (preferably metallic). Stents may be placed by percutaneous or endoscopic routes. Segment III biliary bypass done to relieve malignant jaundice is now obsolete with advanced non-operative techniques of drainage. However, it may still be helpful for a select few patients in a resource-constraint environment.

Few patients experience gastric outlet obstruction due to direct tumor infiltration or compression from surrounding lymph nodes and they may need a gastrojejunostomy.

The aim of all the above interventions is to improve the quality of life in patients with otherwise limited treatment options and poor prognoses.

2 Cholangiocarcinoma

2.1 Introduction

The term cholangiocarcinomas (CCAs) refers to all the tumors arising from the biliary ductal system. As per the anatomical location, they are divided into intrahepatic, perihilar, and distal. Intrahepatic CCAs present as liver masses while Perihilar CCA also known as Klatskin's tumor involves the confluence of the left and right ducts and usually both intra- and extrahepatic ducts [91]. Distal CCAs involve the common and/or proper hepatic duct without extension to the confluence and usually involve the intrapancreatic portion of the bile duct. The perihilar CCAs are the most common subtype (67%), followed by distal (27%), and then intrahepatic (6%). Most intrahepatic CCAs are mass forming, while perihilar have periductal infiltrating growths, and distal CCAs have intraductal growths. The majority of CCAs are adenocarcinomas and are subdivided into three histologic subtypes: sclerosing, nodular, and papillary with papillary carrying the best prognosis. Ninety-five percent of perihilar CCAs are sclerosing variants with very low resectability rates.

CCAs are slow-growing tumors with infiltration along the wall of ducts and extending to surrounding structures. Management is difficult due to associated biliary obstruction and subsequent risk of cholangitis and liver failure. One and two-year survival following diagnosis are 25% and 13%, respectively, with few reported long-term survivors. A 5-year survival rate of 25–30% has been reported in patients with R0 resection [92].

2.2 Etiology and Risk Factors

The incidence of CCAs increases with age, and the majority of patients are 65 years and older. The peak incidence is in the eighth decade of life. Men are affected more commonly than women. Risk factors for CCAs are associated with chronic inflammation of the biliary duct epithelium.

2.2.1 Primary Sclerosing Cholangitis

Patients with primary sclerosing cholangitis have a lifetime risk of about 10% and 1.5% per year from the onset of the disease. They usually present with multifocal disease due to the involvement of several ducts.

2.2.2 Choledochal Cysts

Congenital choledochal cysts increase the risk of cancer due to associated inflammation and bacterial infection. Approximately, 15–20% of patients with unexcised cysts or cysts treated with biliary bypass develop CCA. Complete surgical removal in childhood reduces the chances of malignancy in later life.

2.2.3 Liver Fluke Infestation

biliary parasites such as Opisthorchis viverrini and Clonorchis sinensis contribute to increased risk, especially in Southeast Asia, where incidence can reach 87 per 100,000.

2.2.4 Others

Chronic ulcerative colitis, liver infection, exposure to carcinogens (including thorium dioxide, asbestos, radon, dioxin, nitrosamines, and cigarette smoke), chronic intrahepatic stones, and Hepatitis C are associated with increased risk of CCA [93].

2.3 Clinical Features

Most patients have non-specific symptoms and therefore difficult to diagnose. Painless jaundice is the commonest complaint of patients with CCA and is seen in about 70–90% of patients, followed by pruritis (66%), abdominal pain, weight loss (30–50%), and fever in about 20% [92, 94]. Jaundice occurs early with distal and hilar CCAs, but late with intrahepatic CCAs [95] where it is a marker of advanced disease.

2.4 Diagnosis and Work-Up

The differential diagnosis of cholangiocarcinoma includes benign strictures (post-operative bile duct injury, choledocholithiasis, primary sclerosing cholangitis, recurrent pyogenic cholangitis, ischaemic cholangitis, Mirrizi's syndrome and other malignancy like diffuse intrahepatic metastasis or metastatic hilar lymph node. Therefore, a good knowledge of these mimicking diseases along with clinical and imaging findings is necessary for diagnosis of cholangiocarcinoma. In patients with early resectable disease histological diagnosis should not be mandatory before surgery [93].

2.5 Imaging

USG: Ultrasonography of the abdomen is the first investigation ordered in a patient presenting with obstructive jaundice. Ultrasound may demonstrate biliary duct dilatation and larger hilar lesions. Small lesions and distal CCAs cholangiocarcinomas are difficult to visualize.

Magnetic resonance imaging (MRI)/magnetic resonance cholangiography (MRCP) should be performed to define the appearance and location of the bile duct stricture and determine the type of block. Irregular strictures at the confluence are consistent with the diagnosis of hilar cholangiocarcinoma.

Helical multi-detector computed tomography (CT) is also accurate in diagnosing the level of biliary obstruction. It may demonstrate ductal dilatation and mass lesions. The CT scan will usually demonstrate thickening of the bile duct at the level of obstruction with dilated ducts proximal to it [96]. Three-dimensional helical CT cholangiography can also help in assessing vascular invasion and nodal involvement preoperatively [97].

Positron emission tomography (PET)—computerized tomography (CT) could lead to a change in surgical management in 25% of cases with the detection of unsuspected distant metastases [98]. It has limited sensitivity for infiltrating lesions as the density of metabolically active cells in the setting of intense fibrosis is less. Moreover, inflammation due to benign causes may give rise to false positive results.

Cholangioscopy either perorally or by percutaneous approach provides direct visualization of biliary epithelium, a more targeted biopsy compared with fluoroscopy-guided forceps biopsy, and thus may facilitate tissue acquisition for diagnosing suspected malignant biliary strictures. It has a high technical and procedural success rate for the visualization of biliary lesions improving the diagnosis of biliary strictures. Cholangioscopy may be considered after prior negative conventional sampling.

2.6 Biopsy and Cytology

Due to low yield and sensitivity, it may be reasonable to proceed to surgery without tissue diagnosis. Patients with symptomatic jaundice should undergo biliary drainage preoperatively to allow the liver to recover before resection. For distal strictures or in palliative cases ERCP should be performed which helps in visualization of the proximal duct, stenting of the obstruction, and also to obtain brush cytology. Perihilar strictures should be managed with a percutaneous transhepatic cholangiographic approach.

Endoscopic ultrasound-directed fine-needle aspiration has an accuracy of 91%, sensitivity of 89%, and specificity of 100% in the diagnosis of patients with perihilar CCA [99]. These tumors are often hypocellular and difficult to diagnose by cytology or biopsy.

2.7 Staging

The tumor-node-metastasis (TNM) system eighth edition 2017 devised by the American Joint Committee on Cancer is used for staging cholangiocarcinoma [100]. Bismuth developed a classification system for surgeons to define the extent of biliary resection, however, it lacks the information on the presence of vascular involvement, and parenchymal atrophy (Fig. 5) which can be accessed at https://www.nejm.org/doi/full/10.1056/nejm199910283411807

Type I	Tumor involves the common hepatic duct
Type II	Tumor involves the bifurcation of the common hepatic duct
Type IIIa	Tumor involves the right hepatic duct
Type IIIb	Tumor involves the left hepatic duct
Type IV	Tumor involves both the right and left hepatic ducts

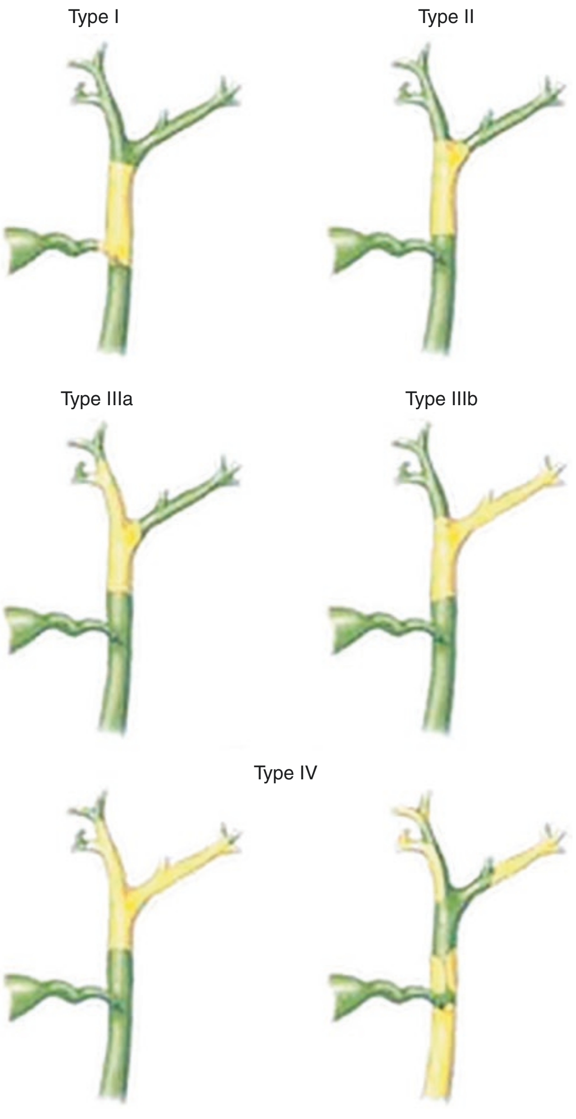
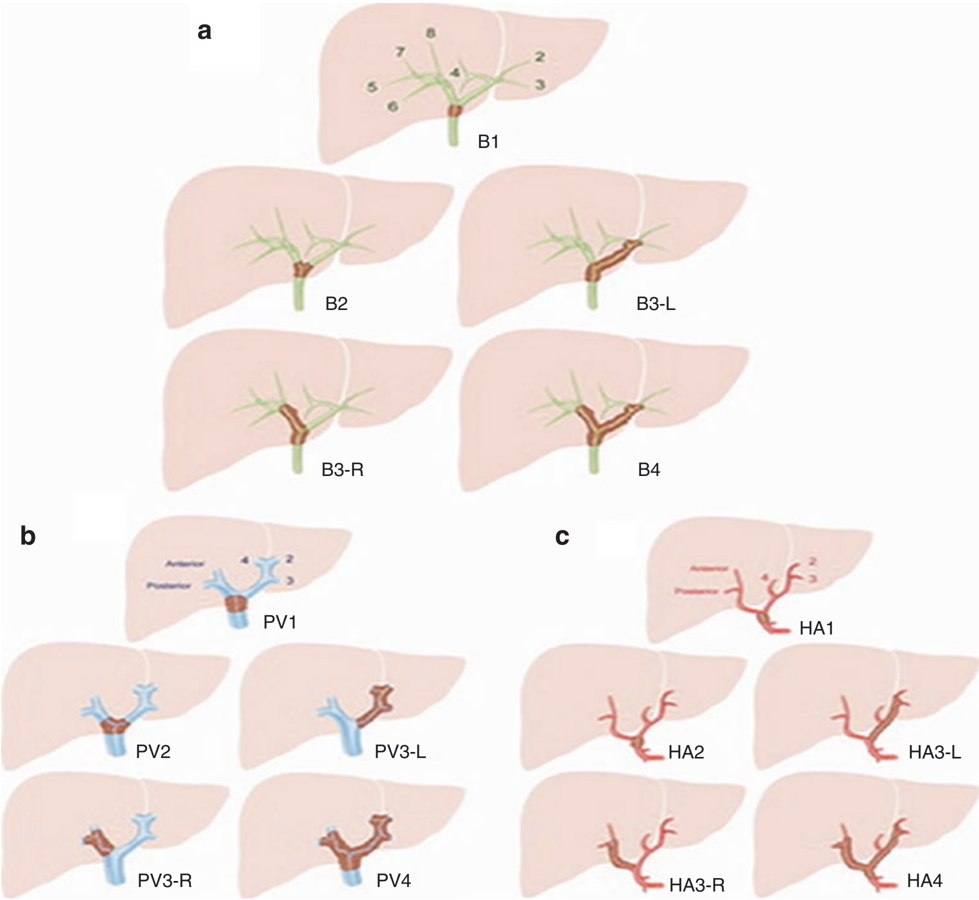


Fig. 5 Bismuth classification of perihilar CCA

Fig. 6 New staging system



A new staging system incorporating tumor size, extent of disease in the biliary system, involvement of hepatic artery and portal vein, nodal involvement, distant metastases, and the volume of remnant liver after resection has been reported (Fig. 6) [101].

2.8 Treatment

2.8.1 Pre-Operative Management

Pre-Operative Biliary Drainage

Even though the advantage of pre-operative biliary drainage (BD) is not demonstrated, there is a trend to consider BD in three situations: (1) when future liver remnant is less than 40% of the total liver volume and if portal vein embolization is considered; (2) cholangitis resistant to antibiotics; (3) renal failure or malnutrition due to hypoalbuminemia. The disadvantages are the subsequent bacterial colonization of bile and cholangitis, which may delay surgery [102]. The stent itself may lead to a dense fibrous reaction that can be difficult to differentiate from the tumor.

2.9 Surgery

Complete surgical resection is the only therapy to afford a chance of cure (Fig. 7). Unfortunately, only 10% of patients present with early-stage disease and are candidates for curative resection.

2.9.1 Intrahepatic CCA

The goal of resection is to remove all liver parenchyma at risk based on the proximal extent of the tumor. Usually, this requires partial hepatectomy or lobectomy for intrahepatic tumors. The presence of lesions in the contralateral lobe and distant metastases portends a poor prognosis and is considered a contraindication to resection.

2.9.2 Hilar CCA

Resection of the involved intra- and extra-hepatic bile ducts, as well as the associated liver segments and caudate lobe along with complete peri-portal lymphadenectomy, is the standard of care. Curative resection with histologically negative margins (R0) is associated with a median survival of 27 months to 58 months and 5-year survival rate of 27–45%, as

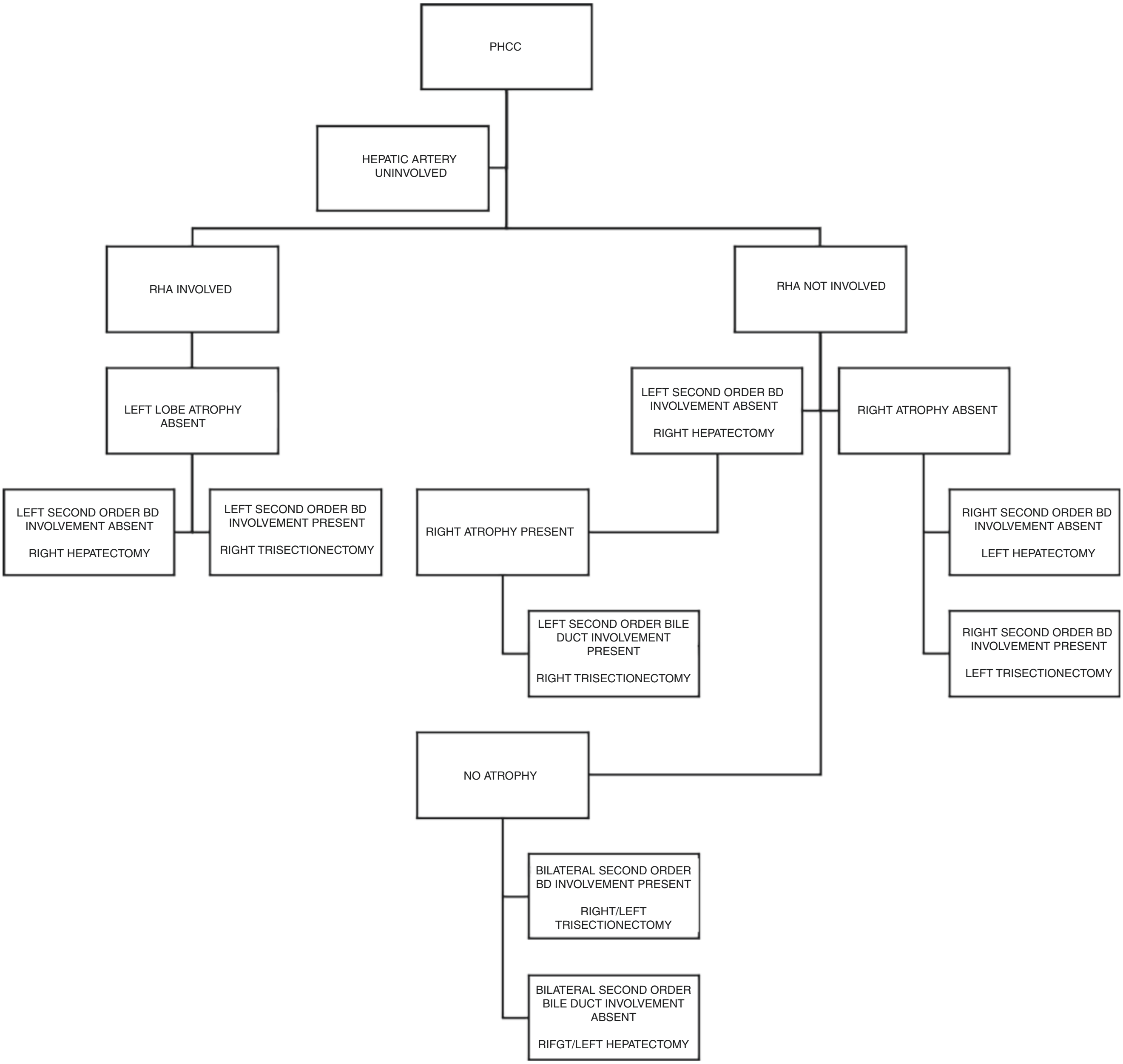

PHCC
HEPATIC ARTERY UNINVOLVED
RHA INVOLVED
RHA NOT INVOLVED
LEFT LOBE ATROPHY ABSENT
LEFT SECOND ORDER BD INVOLVEMENT ABSENT
RIGHT HEPATECTOMY
RIGHT ATROPHY ABSENT
LEFT SECOND ORDER BD INVOLVEMENT ABSENT
RIGHT HEPATECTOMY
LEFT SECOND ORDER BD INVOLVEMENT PRESENT
RIGHT TRISECTIONECTOMY
RIGHT ATROPHY PRESENT
RIGHT SECOND ORDER BD INVOLVEMENT ABSENT
LEFT HEPATECTOMY
LEFT SECOND ORDER BILE DUCT INVOLVEMENT PRESENT
RIGHT TRISECTIONECTOMY
RIGHT SECOND ORDER BD INVOLVEMENT PRESENT
LEFT TRISECTIONECTOMY
NO ATROPHY
BILATERAL SECOND ORDER BD INVOLVEMENT PRESENT
RIGHT/LEFT TRISECTIONECTOMY
BILATERAL SECOND ORDER BILE DUCT INVOLVEMENT ABSENT
RIFGT/LEFT HEPATECTOMY

Fig. 7 Flow chart for surgical decision making [103]

compared to 12 months to 21 months and 0–23% in the presence of histologically positive margins (R1) [104, 105].

Criteria for Unresectability of Hilar CCA [106]

The criteria that determine unresectability in hilar CCA are a requirement of biliary reconstruction options and adequate future liver remnant. Any of the following criteria can categorize hilar cholangiocarcinoma as unresectable:

- Bilateral segmental ductal extension (type IV involvement).
- Unilateral atrophy with either contralateral segmental ductal or vascular inflow involvement.
- Unilateral segmental ductal extension with contralateral vascular inflow involvement.

Staging laparoscopy has a yield of 27% to detect peritoneal or liver metastases and avoids unnecessary laparotomy [106]. Staging laparoscopy should be performed in all patients before exploratory laparotomy.

In patients eligible for resection, a choice between a right-sided and a left-sided hepatectomy is made depending on the involvement of second-order bile ducts or lobar atrophy. Right-sided resections are performed more frequently compared to left-sided ones with no difference in R0 resection rates, survival, or portal vein reconstructions. Hepatic artery reconstructions are needed more frequently with left hemihepatectomy due to the close anatomic relation of the right hepatic artery to the bile duct bifurcation.

Studies demonstrate that 46% of perihilar CCA microscopically involve the caudate lobe with a five-fold increase in R1 resection rates when caudate lobectomy is omitted. Therefore, caudate lobe excision should always be performed for perihilar cholangiocarcinoma.

Recently parenchymal-sparing approaches such as “Taj Mahal resection”, “combined caudate lobe and high hilar resection (CCHR)” or “dumbbell form resection (DFR)” are being propagated which involve anatomic or nonanatomic resection of segments I and IV and V with en-bloc extrahepatic bile duct resection.

Postoperative complications include wound infection, liver or subphrenic abscess, cholangitis, pulmonary embolus, gastrointestinal hemorrhage, and small bowel obstruction with mortality rates up to 5–10%.

2.9.3 Liver Transplantation

If a positive margin or inadequate future liver remnant is anticipated, a liver transplant should be considered for nonmetastatic hilar cholangiocarcinoma. The Mayo Clinic protocol can be used utilized using neoadjuvant chemoradiation followed by liver transplant [107].

In a multicenter study from the United States evaluating the role of neoadjuvant chemoradiotherapy and transplant, post-transplant 5-year recurrence-free survival was 65% [108].

However, very few patients meet the criteria for this option. The inclusion criteria include unresectable perihilar cholangiocarcinoma 3 cm or less in radial diameter without intrahepatic or extrahepatic metastases. Patients with perihilar cholangiocarcinoma developing in a background of primary sclerosing cholangitis should be treated, when possible, with liver transplantation.

2.10 Adjuvant Therapy

2.10.1 Radiotherapy

In general, postoperative adjuvant radiotherapy reduces the risk of local recurrence and potentially improves survival. A recent meta-analysis of 44 studies including patients undergoing resection for extrahepatic biliary tract carcinomas found that adjuvant radiotherapy was associated with improved overall survival with a hazard ratio (HR) of 0.62 (95% CI 0.48–0.78, $P = <0.001$) after exclusion of studies with ampullary or gallbladder cancer patients [109]. Low rates of radiation-induced toxicity were noted.

Postoperative adjuvant radiotherapy for biliary tract cancer can be administered either by external-beam radiotherapy (EBRT), brachytherapy, intraoperative radiotherapy (IORT), or a combination of radiotherapy modalities.

2.10.2 Combined Chemo-Radiotherapy

Preliminary results from the Southwest Oncology Group (SWOG)-S0809 phase II study of adjuvant capecitabine plus gemcitabine followed by concurrent capecitabine with radiotherapy in radically resected CCA and GBC were presented at the 2014 ASCO meeting [110]. Eligibility criteria included R0 resection for patients included extra-hepatic cholangiocarcinoma or gallbladder cancer, lymph node-positive disease, and R1 resections. Of 79 patients, 62% were extrahepatic CCA, and 86% completed planned therapy. Grade 3 or 4 toxicity rate was 64% overall (particularly neutropenia and hand-foot syndrome). For the patients with extrahepatic cholangiocarcinoma ($n = 49$) the 2-year overall survival, 2-year disease-free survival, and local relapse was 66% (95% CI 50–78), 51% (95% CI 36–65), and 11% (95% CI 2–21), respectively.

In summary, despite the lack of conclusive evidence in support of adjuvant therapy, chemoradiotherapy is recommended for patients who have had a resection with curative intent, especially when the tumor has invaded into or through the muscularis layer, the margins of resection are involved, or regional lymph nodes are involved.

European Society of Medical Oncology (ESMO) practice guidelines recommend adjuvant (5-FU-based) chemotherapy for patients with GBC and the possible use of chemoradiotherapy for cholangiocarcinoma where local relapse rates were estimated to reach 52% [111].

2.10.3 Chemotherapy

The most relevant studies in the adjuvant setting are ESPAC-3, BILCAP, and a meta-analysis. European Study Group for Pancreatic Cancer-3 trial [112], the largest randomized trial was conducted in patients with resected periampullary adenocarcinomas. Four hundred and twenty-eight patients with periampullary malignancies (96 bile ducts) were randomly assigned to one of three arms: observation, 6 months of leucovorin-modulated FU, or single-agent gemcitabine. The use of adjuvant treatment was associated with a statistically non-significant survival advantage (median 43 months vs. 35 months, HR 0.86, 95%CI: 0.66–1.11). On multivariate analysis, correcting for prognosis factors, survival benefit for chemotherapy was seen specifically for gemcitabine, and with a better safety profile [112].

BILCAP is a multi-center prospective, randomized phase III trial trying to examine the role of adjuvant chemotherapy with an oral fluoropyrimidine (capecitabine) in patients following potentially curative surgical resection of a biliary tract cancer.

The meta-analysis including 6712 patients has shown that the improvement in 5-year survival with any adjuvant therapy was not statistically significant [pooled odds ratio (OR) = 0.74, 95%CI: 0.55–1.01] compared with surgery alone. However, the survival benefit from adjuvant therapy was statistically significant when the data from the two large registry series (*n* = 1233 patients) were excluded (OR = 0.53, 95%CI: 0.39–0.72). There is a statistically significant overall survival advantage for adjuvant therapy in node-positive disease (OR = 0.49, 95%CI: 0.30–0.80) and margin-positive disease (OR = 0.36, 95%CI: 0.19–0.68) [113].

Please refer to the GBC section for adjuvant chemotherapy.

2.11 Advanced Disease

2.11.1 Radiotherapy

Conventionally fractionated radiotherapy with or without concomitant chemotherapy is considered the standard treatment option for inoperable cholangiocarcinoma. One-year actuarial loco-regional control rates on the order of 60%, were observed at M.D. Andersen [114], and extending up to 75%, at the University of Michigan [115]. The corresponding median overall survival rates in these series were 10 and 13 months, respectively.

2.11.2 SBRT in Unresectable Cholangiocarcinoma

Improved local control and survival rates have been observed with higher radiotherapy doses suggesting dose escalation like SBRT as a promising therapeutic approach in the treatment of unresectable bile duct cancer [116].

2.11.3 Chemotherapy

In patients with advanced biliary tract cancer, the survival benefit of chemotherapy over best supportive care alone was suggested in a trial that randomly assigned 90 patients with advanced pancreatic or biliary cancer (37 with bile duct cancer) to 5-FU-based systemic chemotherapy with leucovorin and etoposide versus best supportive care alone (median survival 6 vs. 2.5 months respectively) [86].

The superiority of the combination gemcitabine-cisplatin regimen is shown in the recently published ABC Trial. A combination of gemcitabine and cisplatin improved overall survival and progression-free survival by 30% more than gemcitabine alone. Based on these results, the combination of gemcitabine plus cisplatin is considered the standard of care as first-line chemotherapy for biliary tract cancer treatment [117].

2.12 Palliative Measures

The goal of palliation for bile duct tumors is drainage of the biliary system to avoid jaundice. In many cases, patients will die of liver failure as a direct result of inadequate biliary drainage. Drainage of the bile ducts can be performed using ERCP-placed stents, or PTC-placed stents. Hilar CCAs are best palliated using PTC-placed stents. A small, multicentered randomized controlled trial was performed comparing PTC stents alone with PTC stents plus photodynamic therapy (39 patients total) [118]. Patients receiving photodynamic therapy survived 493 days compared with 98 days for those treated with stenting alone. This suggests a role for photodynamic therapy in these patients. Distal bile duct tumors can be successfully palliated with an ERCP-placed stent.

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Liver Cancer

Melroy Alistair D'Souza, Mahesh Goel,
and Shraddha Patkar

Abbreviations

AASLD	American Association for the Study of Liver Disease
AFP	Alpha-fetoprotein
ALPPS	Associated liver partition and portal vein ligation for staged hepatectomy
BCLC	Barcelona Clinic Liver Cancer
CEUS	Contrast-enhanced ultrasound
CLIP	Cancer of the Liver Italian Program
CT	Computerized tomography
CTP	Child–Turcotte–Pugh
CUPI	Chinese University Prognostic Index
CVP	Central venous pressure
DCP	Des-gamma-carboxyprothrombin
DDLT	Deceased donor-related transplant
EASL	European Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
FLR	Future liver remnant
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIFU	High-intensity focused ultrasound
HIV	Human immunodeficiency virus
HKLC	Hong Kong Liver Cancer
HVPG	Hepatic venous pressure gradient
IRE	Irreversible electroporation
JIS	Japanese Integrated Scoring
LDLT	Living donor-related transplant
MDCT	Multidetector CT
MELD	Model for end-stage liver disease
MWA	Microwave ablation
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
OLT	Orthotopic liver transplantation
PBC	Primary biliary cirrhosis
PDGFR	Platelet-derived growth factor receptor
PEI	Percutaneous ethanol injection
PVE	Portal vein embolization
PVL	Portal vein ligation
RECIST	Response evaluation criteria in solid tumors
RFA	Radio frequency ablation
SBRT	Stereotactic body radiation therapy
SLT	Salvage liver transplantation
TACE	Transarterial chemoembolization
TAI	Transarterial chemoinfusion
TARE	Transarterial radioembolization
TNM	Tumor–node–metastasis
UNOS	United network for organ sharing
US	Ultrasound
VEGFR	Vascular endothelial growth factor receptor

1 Introduction

Primary cancer of the liver includes hepatocellular carcinoma (HCC), cholangiocarcinoma, hepatoblastoma, sarcomas, hemangioendothelioma and primary lymphomas. HCC accounts for more than 90% of liver cancer, and the main risk factor for its development is liver cirrhosis of any etiology. Clinical presentation is variable, and patients may remain asymptomatic for a long time, presenting with symptoms only when the disease is advanced. When diagnosed at an early stage, it usually incidental or when patients with cirrhosis are on a surveillance program. Imaging is the cornerstone in diagnosis, management and follow-up of these patients.

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The prognosis of advanced untreated HCC is dismal with a median survival of 8 months [1]. Prognosis in general depends on whether curative treatment can be given, which is in turn dependent on the tumor burden, liver function and the patient's performance status. Curative treatment in the form of resection, liver transplantation or ablation is associated with a 5-year survival of 40–70%.

HCC will be dealt with here and biliary cancers in a separate chapter.

2 Epidemiology and Etiology

2.1 Epidemiology

HCC is largely a problem of the developing world where majority of the new cases occur. It is the fifth most common cancer in men and the ninth in women but the disparity in rates between the sexes is not well understood. Globally, the distribution of HCC varies by region, sex and etiology. The regions with the highest age-adjusted incidence rates are Eastern and South-Eastern Asia and sub-Saharan Africa. Intermediate rates occur in Southern Europe and Northern America and the lowest rates are in Northern Europe and South-Central Asia [2].

In India, information on HCC epidemiology is unreliable. Based on cancer registries in five Indian urban populations (Mumbai, Bangalore, Chennai, Delhi and Bhopal), liver cancer ranks as the fifth most frequent cancer for both sexes [3]. However, the cancer registries in India probably do not provide accurate estimates of HCC prevalence due to the heterogeneous nature of information sources. Age-adjusted incidence rate of HCC in India for males ranges from 0.7 to 7.5 and for females from 0.2 to 2.2/100000 per year and the male-to-female ratio for HCC in India is 4:1 [4].

2.2 Etiology

Chronic injury and inflammation seem to be the pathological processes leading to HCC development regardless of etiology and liver cirrhosis is the underlying pathology in the majority of HCCs. The cell death in liver cirrhosis leads to a chronic stimulus for cell division and the formation of regenerative noduli. This in turn leads to DNA changes, dysplasia and subsequently malignant transformation. The etiology can be viral, toxic or metabolic.

1. Chronic hepatitis B (HBV) and C (HCV) virus infection account for more than 80% of HCC cases. Both HBV and HCV infected individuals run a significantly greater risk of developing HCC as compared to a noninfected population. This risk is increased in infected individuals when other risk factors coexist including male sex, older age, coinfection with the other hepatitis virus or human immunodeficiency virus (HIV), presence of diabetes mellitus, obesity, chronic alcohol consumption and tobacco smoking [4].
2. Alcoholic liver disease causes fatty liver and hepatitis leading eventually to cirrhosis and HCC development. Several studies have confirmed a confirmed a dose-dependent effect of alcohol consumption on the risk of HCC and there seems to be no safe limit for the effects of alcohol on the liver. Alcohol acts in synergy with other risk factors for chronic liver disease in the development of HCC [5]. In India, HBV and HCV infection and alcohol consumption are the main causes of HCC [6].
3. Obesity, diabetes and metabolic syndrome have been consistently related to a raised incidence of HCC. This increased risk may be mediated through the development of nonalcoholic fatty liver disease (NAFLD) or these factors may act directly and mediate carcinogenesis without the development of cirrhosis. A significant proportion of patients with nonalcoholic steatohepatitis (NASH) and HCC have noncirrhotic livers [7]. Worldwide the incidence of HCC is likely to increase related to the epidemics of HCV infection, alcohol abuse, obesity, type-2 diabetes mellitus and the metabolic syndrome.
4. Other causes: Aflatoxin exposure, exposure to colloidal thorium dioxide (Thorotrast), primary biliary cirrhosis (PBC), autoimmune hepatitis, Wilson's disease, Budd–Chiari syndrome, hemochromatosis, acute intermittent porphyria, hereditary tyrosinemia, a-1-antitrypsin deficiency and glycogen storage disease type 1. All of these have in common a chronic inflammation related to the hepatocellular injury.

3 Clinical Presentation

HCC is usually diagnosed in an advanced stage. Small tumors amenable to curative treatment are usually discovered in patients under surveillance or incidentally on abdominal imaging for other conditions. Early symptoms are often vague and nonspecific. Due to the liver's large functional reserve HCC may thus progress insidiously and escape early diagnosis.

Right upper quadrant pain, mass and weight loss is the classic clinical triad of HCC. Fever of unknown origin is a common symptom. General symptoms of malignancy such as anorexia, nausea, lethargy and weight loss are often present at diagnosis. Symptoms and signs are both cancer-related and due to the underlying liver disease and function. When advanced the patient may present with hepatomegaly and signs and symptoms of hepatic decompensation like ascites, jaundice, edema, encephalopathy and gastrointestinal bleeding [8]. For many patients the diagnosis of HCC is also the first presentation of their undiagnosed cirrhosis. Variceal hemorrhage is a poor prognostic sign. Jaundice when present could be due to hepatic insufficiency or due to biliary obstruction and this distinction has prognostic significance. Liver failure may occur when the tumor invades the portal vein or the hepatic veins and in rare cases may present with Budd-– syndrome. A rare and dramatic presentation of HCC is tumor rupture presenting with abdominal pain, tenderness and hemodynamic instability. Even more uncommon is the occurrence of paraneoplastic syndromes in HCC like hypoglycemia, erythrocytosis, hypercalcemia and hypercholesterolemia [9].

4 Surveillance and Diagnostic Evaluation

The diagnosis of HCC is primarily radiological and laboratory evaluation can be used as a complement. The use of biopsy is limited to when the diagnosis is uncertain and carries with it the risk of complications like bleeding and needle-track seeding. Diagnostic algorithms and guidelines published by European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Disease (AASLD) have been used in the diagnostic evaluation and treatment of HCC [10–12]. The Japan Society of Hepatology has also published guidelines [13].

4.1 Surveillance

HCC-surveillance involves the application of repeated screening to a group of patients considered high risk, to detect and treat HCC at an early stage and thus improve outcomes. This is usually done at fixed time intervals. Tumor doubling time in HCC varies widely in literature but in most western studies is usually 4–6 months and 6 months is the usual time interval for screening [14]. Factors that should be taken into consideration if a patient is to undergo surveillance include liver function, performance status, comorbidity and compliance so that if HCC is detected, it can lead to a curative treatment. Only then is surveillance meaningful. All patients with cirrhosis regardless of etiology with Child–Turcotte–Pugh (CTP) class A-B should be included in a surveillance program. Patients with CTP class C have poor survival and unless on a transplant waiting list should not be included in surveillance. Noncirrhotic HBV carriers with active hepatitis and chronic HCV patients with advanced fibrosis are also considered high risk and should be followed up [12].

High-quality ultrasound (US) at 6-monthly intervals is the recommended modality by both EASL and AASLD [10, 11]. US has a high specificity and acceptable sensitivity but is highly operator dependent [15]. It is noninvasive and has no complications. The routine use of contrast agents in US is not backed by evidence. Both computerized tomography (CT) and magnetic resonance imaging (MRI) have higher sensitivity and specificity than US but have a high cost and risks including radiation and contrast-related complications. They are not recommended as routine screening modalities and are used only when US is not feasible.

Serum alpha-fetoprotein (AFP) is the most widely tested biomarker in HCC. As a surveillance tool, it however lacks sensitivity and specificity and is not routinely recommended [16]. AASLD recommends use of AFP in conjunction with US for surveillance [12]. When used in combination with US for surveillance, the cut-off value of AFP should be set at 200 ng/mL [4]. The use of other serum markers like des-gamma-carboxyprothrombin (DCP) and glycosylated AFP (L3 fraction) is not recommended for surveillance.

4.2 Diagnostic Evaluation

Detection of HCC at an early stage has a significant impact on improving prognosis and survival in these patients (Fig. 1) [17]. The pathological processes underlying the development of HCC include angiogenesis, changes in cellularity and decrease in the number and function of Kupffer cells. Among these, the vascular alterations seen in the nodules, specifically increased arterial flow and decreased portal flow, are particularly important as far as diagnosis is concerned [18, 19]. While regenerative nodules and dysplastic nodules have a vascularity derived from the portal circulation, HCC development involves neovascularization primarily of arterial derivation. This forms the basis of radiological diagnosis using contrast-enhanced dynamic imaging like contrast-enhanced ultrasound (CEUS), CT and MRI. While US is used as a screening test, it is not diagnostic in the evaluation of HCC. For this, four-phase, multidetector CT (MDCT) and dynamic contrast-enhanced MRI including late hepatic arterial, portal venous and delayed phase imaging, 3–5 min after contrast administration are the recommended radiological modalities for HCC [20–22]. The “radiological hallmark” of HCC during dynamic imaging is the presence of arterial enhancement, followed by wash out of the contrast from the tumor in the portal venous and/or delayed phases [10, 11]. Detailed criteria for radiological diagnosis have been developed by the American College of Radiology and called the Liver Imaging Reporting and Data System (LI-RADS) [23]. These radiological criteria are however applicable only in the presence of cirrhosis and when the lesion size is greater than 1 cm.

Lesions smaller than 1 cm in size should be followed up at 4-monthly intervals with US. When a lesion measures

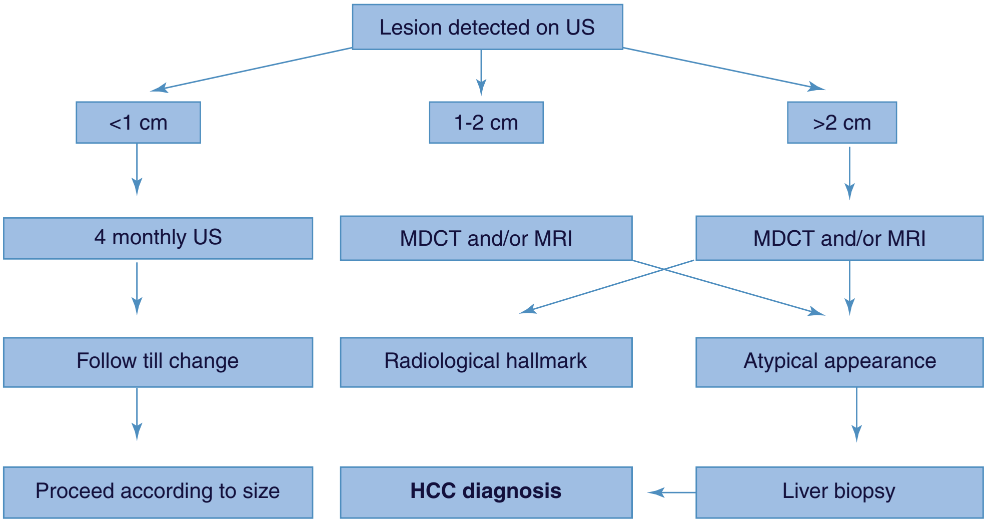

Fig. 1 Diagnostic algorithm for HCC. Adapted from the EASL-EORTC guidelines [10]

1–2 cm and shows the typical HCC "radiological hallmark," i.e., contrast uptake in the arterial phase and washout in the venous/late phase then one imaging modality either CT or MRI can be used for a definitive diagnosis. Most often however a second imaging modality in conjunction with serum AFP and biopsy is needed for diagnosis. If biopsy is negative CT or MRI follow-up is recommended at 3–6-month intervals till changes on imaging are noticed after which a new biopsy is warranted.

Lesions greater than 2 cm in size in the setting of cirrhosis are most often HCC and when the "radiological hallmark" is present, a single imaging modality, either CT or MRI is adequate for a diagnosis. Biopsy may be required if the imaging is atypical. It is worthy of note that approximately 8% of HCC lesion less than 3 cm in size are hypovascular on imaging [24].

In the setting of HCC in a noncirrhotic liver, diagnosis is often made late due to the lack of symptoms. Tumors at diagnosis are large and on imaging are well encapsulated and have a lobulated appearance, showing intense arterial contrast enhancement and sometimes areas of necrosis and bleeding. Even here biopsy maybe sometimes needed for a definitive diagnosis [25].

The complete radiological evaluation in a patient of HCC should include information on the presence and degree of cirrhosis, the presence of portal hypertension and the size, number and location of the tumorous lesions. In addition, vascular or biliary involvement, portal venous thrombosis, lymphadenopathy and the presence of distant metastases should be noted. These variables are essential for accurate staging and have a great impact of the decision making in treatment.

The use of liver biopsy in diagnosis of HCC is not routinely recommended due to risk of bleeding, false negatives and needle-track seeding [26, 27]. Lesions smaller than 1 cm should not be biopsied due to the high risk of sampling error and false negatives. Biopsy should be considered in lesions greater than 1 cm when a diagnosis cannot be established based upon at least two high-quality imaging modalities (MDCT and MRI) according to the EASL-AASLD criteria.

AFP is the most commonly used tumor marker in HCC. It however has both low sensitivity and specificity and is not usually recommended for diagnostic purposes but may be used sometimes as an adjunct. It may, however, be used as a prognostic factor and can sometimes be used to evaluate treatment response.

5 Staging and Treatment Strategy

The value of staging HCC lies in disease prognostication and thus enabling selection of the most appropriate treatment strategy for the patient. It helps in evaluating treatment outcomes and to compare data for research. Outcome in HCC is the product of multiple factors and these should be considered when deciding the treatment. Several staging systems exist but the Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely endorsed and accepted system in the management of HCC and will be discussed in detail later [28].

Before making a treatment decision, three factors must be taken into account when a patient with HCC is staged:

1. The extent of the tumor.
2. The patient's general health status.
3. Liver function and the presence of portal hypertension.

The number and size of nodules, the presence of vascular invasion and the occurrence of extra-hepatic metastases define tumor extent. The size of the tumor is often associated with its propensity for microvascular invasion are definite poor prognostic factors. Both the largest tumor diameter and the total tumor burden have prognostic importance. Micro- and macrovascular invasion of the portal and hepatic veins are indications of the ability of the tumor to metastasize. While macrovascular invasion is often considered a contraindication for transplantation, it is unclear how the presence of microvascular invasion should affect treatment decision-making [29, 30].

A patient's general health status plays an important role in determining which treatment can be offered to a patient. The health status includes both performance status and the presence of symptoms. The ECOG/WHO scale was developed by the Eastern Cooperative Oncology Group (ECOG) and is widely used as a measure of the patient's performance status and is included in BCLC staging system [31, 32].

Liver function is most commonly evaluated by the Child–Turcotte–Pugh (CTP) score. It is a simple and widely used grading system for liver function and categorizes patients into three groups A, B and C according to deteriorating liver function (Table 1). A big disadvantage of CTP score is the presence of subjective parameters. Other methods like the MELD score (Model for End-stage Liver Disease), measurement of portal pressure, indocyanine green retention rate measurement have been used with variable success [33, 34]. The MELD score was adopted by the United Network for Organ Sharing (UNOS) in 2002 for prioritization of patients awaiting liver transplantation but it has been criticized for failing to classify patients with advanced liver disease correctly. The measurement of indocyanine green retention at 15 min (ICG R-15) is a well-established method used to estimate liver function especially in Asian countries and is recommended in the decision making for both indication and extent of surgery [4]. Portal hypertension as a prognostic factor has been validated. Direct indicators like measuring the hepatic venous pressure gradient (HVPG) and evaluating for indirect indicators of portal hypertension, viz., esophageal varices, splenomegaly and platelet count <100.000/mm^3 are recommended before surgery [10].

Table 1 The Child–Turcotte–Pugh (CTP) scale

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation (s) *or* INR	<4.0 <1.7	4.0–6.0 1.7–2.3	> 6.0 >2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

CTP Class obtained by adding score for each parameter
Class A—5–6 points
Class B—7–9 points
Class C—10–15 points

5.1 Staging Systems in HCC

Over the years multiple staging systems have been developed and used all over the world. Since 1985, when the Okuda staging system was first published, combining both parameters for tumor and liver function, at least 18 staging systems and guidelines have been published, each having their strengths and drawbacks [35, 36].

For most cancer types, the tumor–node–metastasis (TNM) system is the standard for staging, reporting and comparison of data. In HCC, the eighth TNM edition of the American Joint Committee on Cancer/International Union Against Cancer is currently used [37]. A major drawback with the TNM system in HCC is that it does not include liver function or the patients' health status and that it can be applied only in resected or transplanted patients in the postoperative setting. Its use preoperatively in staging and treatment decision-making is thus limited. The TNM staging system is used mainly for pathological staging and has been validated for this purpose [38].

The Okuda staging system, Cancer of the Liver Italian Program CLIP) score, Barcelona Clinic Liver Cancer (BCLC) stage, French GRETCH, Chinese University Prognostic Index (CUPI), Japanese Integrated Scoring (JIS), Tokyo score and Hong Kong Liver Cancer (HKLC) systems are some of the systems in use. Of these, the BCLC staging system is the most established and validated [39]. The EASL–EORTC and the AASLD guidelines endorse the BCLC classification [10, 11]. The BCLC uses tumor extent, liver function and the patients' health status to categorize patients into 5 groups where groups 0 and A are amenable to potentially curative treatment, groups B and C can receive active palliative treatment and group D, just symptomatic treatment (Fig. 2) [39, 40].

According to the BCLC system, *very early stage HCC* (BCLC stage 0) is defined as the presence of a single tumor <2 cm, without vascular invasion/satellites in patients with ECOG-0 and a with a CTP class A. *Early stage HCC* (BCLC stage A) includes patients with single tumors >2 cm or 3 nodules <3 cm of diameter, with ECOG-0 and CTP class A or B [10]. These patients can be offered curative treatments, including resection, transplantation and ablation achieving good results with median overall survival (OS) more than 60 months and 5-year survival of 50– 75% [10, 41, 42].

The *intermediate stage* (BCLC stage B) comprises patients with multifocal HCC without macrovascular invasion, or extrahepatic spread, with CTP A or B and do not have cancer-related symptoms, with ECOG 0. These patients may be offered palliative treatment, such as trans-arterial

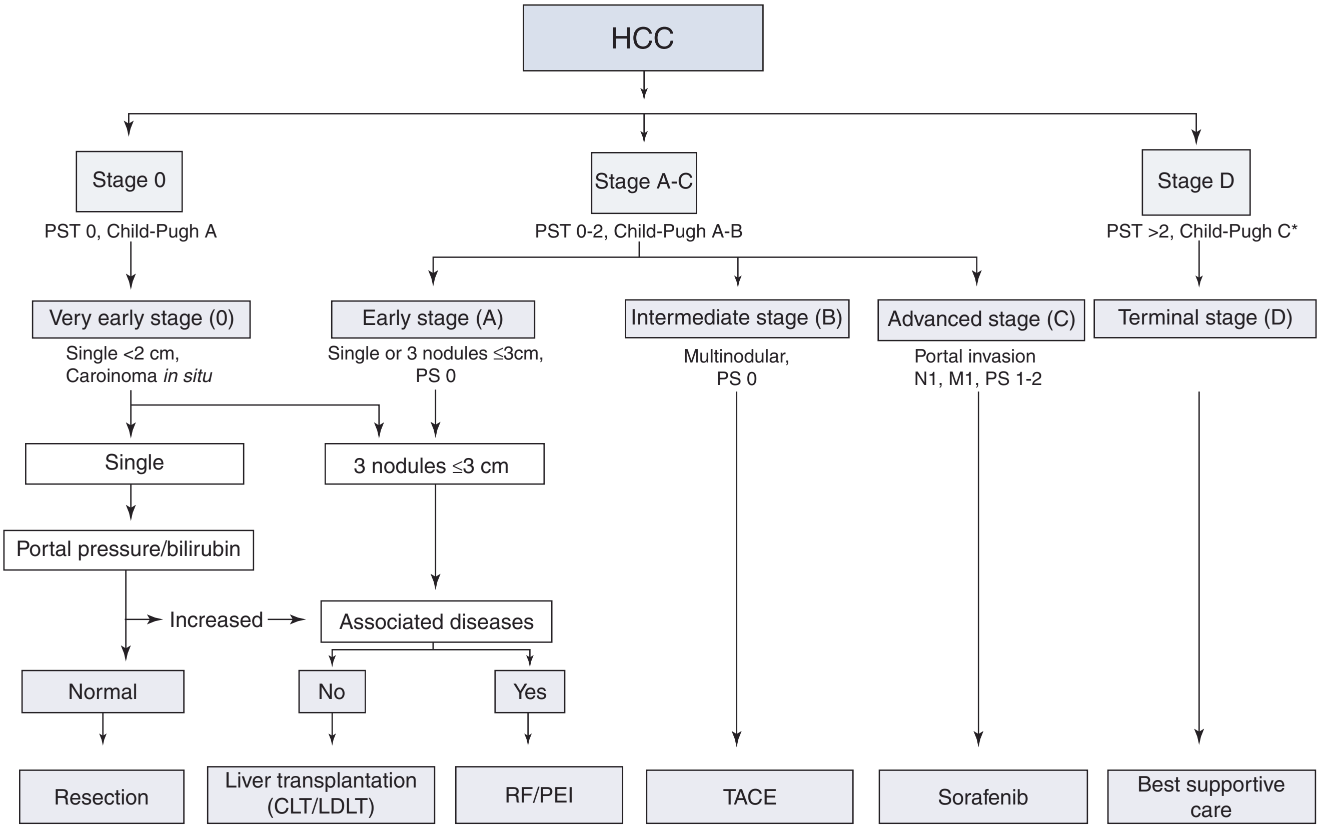
HCC
Stage 0
PST 0, Child-Pugh A
Stage A-C
PST 0-2, Child-Pugh A-B
Stage D
PST >2, Child-Pugh C*
Very early stage (0)
Single <2 cm,
Caroinoma in situ
Early stage (A)
Single or 3 nodules ≤3cm,
PS 0
Intermediate stage (B)
Multinodular,
PS 0
Advanced stage (C)
Portal invasion
N1, M1, PS 1-2
Terminal stage (D)
Single
3 nodules ≤3 cm
Portal pressure/bilirubin
Increased
Associated diseases
Normal
No
Yes
Resection
Liver transplantation
(CLT/LDLT)
RF/PEI
TACE
Sorafenib
Best supportive
care

Fig. 2 The BCLC staging system 2011 [10]

chemoembolization (TACE) and a median survival of up to 20 months with the best responders going up to 36–45 months [43].

The *advanced stage* (BCLC stage C) includes patients who present with macrovascular invasion or extrahepatic spread with lymph node involvement or metastases. Patients are usually symptomatic and have ECOG 1–2. These patients have a very poor prognosis with a median survival of 6 months. This prognosis has been improved somewhat by the introduction of Sorafenib, a multityrosine kinase inhibitor now used in advanced cases and discussed later [44].

Finally, patients with poor general status (ECOG 3–4) and CTP C due to extensive tumor involvement are considered *end stage HCC* (BCLC stage D). Prognosis is dismal and only symptomatic treatment can be offered. Here median survival is 3–4 months [28].

Hong Kong Liver Cancer classification was proposed in 2014 based on the results from a single center cohort of 3856 patients of HCC, predominantly associated with HBV infection. This system more effectively deals with the problems of heterogeneity in the BCLC B and C groups and the rigid allocation of treatment options. It allows for more aggressive management with surgery as an option for BCLC B and TACE as an option for BCLC C groups. It is considered more suitable for the Eastern population with predominantly HBV associated disease [45].

6 Treatment

Decision-making in HCC treatment should always be made in a multidisciplinary setting with hepatologists, surgeons, oncologists, radiologists, interventional radiologists and pathologists involved in the process. Potentially curative treatments in HCC include liver resection, liver transplantation and ablation while palliative treatments include TACE and Sorafenib. Choosing the optimal treatment is controversial and is reflected in the recommendations of the various international HCC guidelines. Deciding which is the optimal is often a matter of debate but resection and transplantation achieve the best outcomes with 5-year survival between 60% and 80% [21]. The BCLC staging system or similar is usually used as a guide to allocate treatment but the final choice depends on local tradition, competence and available resources. Regardless of the treatment algorithm used, the three important factors, tumor extent, health status and liver function should be given careful consideration and the patient staged appropriately.

6.1 Liver Resection

Along with transplantation, resection forms the mainstay of treatment in patients with early stage tumors. It is the treatment of choice in patients with preserved liver function (CTP A), good performance status and when resectability has been evaluated in terms of tumor burden and function of the liver remnant [4].

In noncirrhotic patients, resection is the treatment of choice, with major hepatectomy being performed to achieve "R0" status, with good perioperative outcomes and acceptable survival [46]. In the setting of cirrhosis, strictly following most current treatment guidelines, resection can be offered only to patients with early stage HCC (BCLC stage 0-A). In practice however, both intermediate and advanced stage tumors (BCLC stages B and C) with good performance status and preserved liver function (CTP A and early B) are often considered for resection with good results [47, 48]. In the report by Torzilli et al., 5-year survival rates of 57% and 38% were reported for BCLC B and C patients respectively [47]. Indeed, the BCLC criteria are regarded as too restrictive especially in Asian countries with the Japanese, Korean and Hong Kong algorithms all recommending a more radical approach in adopting resection for more advanced tumors [4].

Serum bilirubin, cirrhosis, esophageal varices, tumor size and macrovascular invasion are independent prognostic factors for overall survival in resected patients [47]. Intrahepatic macrovascular portal or hepatic venous invasion is not a contraindication for surgery but spread outside the liver including lymph node metastases are associated with very poor survival and resection is usually not recommended. In the setting of cirrhosis resection should be considered only when the patient has a good liver function (CTP A) due to the high risk for postoperative liver failure when a major resection is performed.

Complete oncological clearance ideally warrants an anatomical resection for negative margins. Most micrometastases occur within a 2-cm margin from the tumor and the recommendation is to strive for this margin during resection. However, this may not be always possible either due to location of the tumor or due to the need to preserve as much parenchyma as possible in cirrhotic patients. Whether segmental resection is better than atypical resection in HCC is controversial, but an attempt to perform an anatomical resection should always be made [49]. To this end, high quality preoperative imaging in surgical planning is indispensable. Technological advances in liver surgery especially in transection techniques like the ultrasonic dissector have found widespread application but local tradition and availability usually guides which method is used. Laparoscopic resection for HCC is safe and feasible in selected patients and is usually recommended for peripherally located tumors <5 cm in size [50].

Preoperative strategies to increase the future liver remnant (FLR) have been used for HCC with methods like portal vein embolization or ligation (PVE/PVL), sequential TACE and PVE, radioembolization and associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) being used to improve resectability [51]. In the cirrhotic patient with HCC these approaches are however of questionable value due to uncertain hypertrophy of the FLR.

Blood loss during liver surgery has a profound impact on morbidity and mortality. Low central venous pressure (CVP) maintenance, intermittent Pringle maneuver and the use of techniques like the "anterior approach," "Hepatic vascular exclusion" and the "liver hanging maneuver" have all been used to reduce blood loss during liver resection [8].

6.2 Liver Transplantation

Orthotopic liver transplantation (OLT) is the most definitive treatment for HCC removing not only the tumor radically but also the diseased liver and with it. This reduces the risk for recurrence as well as cirrhosis-related morbidity and mortality. Transplantation is the treatment of choice for HCC in patients with poor liver function (CTP B and C), when an organ is available [4].

The well-established "Milan criteria" are widely used as patient selection criteria in terms of tumor burden [52]:

- Solitary nodule ≤5 cm in diameter or,
- ≤3 nodules, ≤3 cm in diameter,
- And without radiological evidence of vascular invasion or distant metastases.

The Milan criteria have been incorporated into the BCLC algorithm and by the UNOS pretransplant staging for organ allocation in the US but are widely regarded as too restrictive [4, 10].

The University of California, San Francisco (UCSF) criteria is the most accepted extension of the Milan criteria and has comparable outcomes [53]:

- Single tumor ≤65 mm in diameter,
- Or 2–3 tumors, each ≤45 mm with accumulative tumor size ≤ 80 mm,
- And without radiological evidence of vascular invasion or distant.

Macrovascular invasion is usually considered a contraindication to transplantation.

In cirrhotic patients with early HCC with good liver function (CTP A) where resection is usually the first choice of treatment, the use of transplant as an alternative is controversial. In Western countries, in the presence of portal hypertension liver transplant is recommended to these patients. In Asia, even if portal hypertension is present these patients with early tumors are usually resected with equivalent outcomes [4, 54]. Decision-making in this situation should always be made in a multidisciplinary setting weighing the pros and cons in each individual case.

The major drawback in offering liver transplantation is the limited availability of organs and long transplant waiting lists with the inherent risk of disease progression leading to drop outs. To circumvent this problem several strategies have been proposed. Living donor-related transplant (LDLT) has the advantage of practically no waiting list if a suitable donor is available. However, it does have an inherent risk of morbidity to the donor with an approximately 2% risk of severe complications and 0.3% mortality [10]. Some studies report an increased recurrence rate in LDLT as compared to deceased donor-related transplant (DDLT) while others report no difference in survival outcomes [55]. As of today, LDLT should be limited to centers of excellence in hepatic surgery and transplantation.

To minimize the drop-outs in the waiting period, the use of "bridge-to-transplantation" therapies in the neoadjuvant setting such as TACE, ablation or radioembolization have gained popularity. Though helpful in reducing the drop rate, their effect on long-term outcomes remains to be seen and further study in this area is needed [56]. Another alternative to primary OLT is the policy of salvage liver transplantation (SLT) in which the patient undergoes surgical resection first and a transplant is offered later for recurrence or due to deterioration of liver function. Outcomes of SLT after resection for HCC may be comparable to primary OLT and is still a feasible option in centers with resource constraints for transplant [57].

6.3 Local Ablation

Local ablative techniques are employed to locally destroy tumors in the liver. Local ablation is recommended for early stage tumors, i.e., CTP class A or B patients with ≤3 tumors each ≤3 cm in diameter (BCLC stage 0-A) in patients who are not suitable candidates for surgery due to age, associated comorbidities, location of the tumor and to some extent liver function [4, 10]. The advantage of local ablation is that less "normal" liver parenchyma is sacrificed and that most often it can be performed percutaneously, thus avoiding open surgery. On the other hand, the drawbacks include possible incomplete tumor destruction, risk for tumor seeding and the limit on the size of tumors that can be ablated. Tumors close to the liver hilum, the central bile ducts and peripheral HCCs close to other organs pose a problem and sometimes preclude ablation. The commonest modalities are radio frequency ablation (RFA), microwave ablation (MWA) and percutaneous ethanol injection (PEI).

PEI was the first described method and was for a long time the standard for local ablation whereby alcohol was injected under image guidance to induce coagulative necrosis in the tumor. PEI has however been superseded by RFA and MWA as the most widely used ablative techniques for HCC due to a high local recurrence rate and inferior survival [58]. It is still, however, used when thermal techniques cannot be applied or as a complement to them.

Both RFA and MWA use thermal energy to induce coagulative necrosis in the tumor. RFA is the most widely studied and available modality for ablation and produces a "safety ring" around the tumor most likely destroying even small microsatellites around it [10]. MWA has an advantage that peritumoral vessels do not reduce its efficacy and the treatment time is shorter than RFA. Both RFA and MWA can be performed percutaneously (US- or CT-guided), laparoscopically and during open surgery depending upon the individual case. Advances in radiology like multimodality fusion imaging have the potential to improve outcomes in ablation. These methods have a low rate of complications and ablation can easily be repeated in case of incomplete effect or recurrence. Essentially RFA and MWA have similar results especially with the introduction of newer generation MWA systems [59]. To evaluate the effect of ablation radiology is usually recommended 4 weeks after the procedure. If done earlier, the reactive hyperemia surrounding the ablation zone can be misinterpreted as incomplete ablation.

Irreversible electroporation (IRE) is a nonthermal ablation technique using electric pulses to induce cell death, at the same time preserving the structural integrity of bile ducts and vessels. IRE seems to be useful for tumors near the major blood vessels or bile ducts but data on this technique is scare [4].

Comparing outcomes after surgery and local ablation is not easy. There have been a several studies comparing ablation and resection for early HCC and the evidence shows that resection has better long-term survival and lower recurrence rate as compared to ablation [60]. Liver resection is however associated with longer hospital stay and higher rate of complications but should be recommended as the first-hand choice. Other ablative methods like cryoablation, laser ablation and high-intensity focused ultrasound (HIFU) have been used but have not gained widespread application [59].

6.4 Transarterial Chemoembolization (TACE) and Other Transcatheter Therapies

TACE is a palliative treatment recommended for HCC in patients with unresectable, large/multifocal HCCs who do not have vascular invasion or extrahepatic spread and with good performance status and relatively preserved liver function (CTP A or B) [4, 10]. The principle of TACE is based on the fact that HCC receives it blood supply almost entirely from the hepatic artery. Thus, chemotherapeutic agents can be delivered in a targeted fashion, and then followed by embolization of the arterial supply. When infusion of chemotherapy is performed without embolization it is called transarterial chemoinfusion (TAI), whereas embolization with radioactive microspheres is called transarterial radioembolization (TARE) or selective internal radiation therapy" (SIRT) [4].

Different chemotherapeutic agents have been used for TACE but the commonest is Doxorubicin. It most often mixed with the contrast agent, lipiodol and delivered through a catheter superselectively placed in the arterial supply of the tumor. After this embolization is carried out by particles like gel foam. Doxorubicin can also be bound to microspheres (drug eluting beads) instead of lipiodol and the procedure is then called DEB-TACE and has fewer side effects than conventional TACE because of less systemic absorption of the chemotherapeutic agent [61]. The protocol for TACE is not standardized and varies depending on the local tradition but is most often repeated at 1–3-month intervals as long as it is technically possible. The first evaluation is recommended by CT or MRI 1 month after treatment.

TACE has demonstrated significant survival benefit in selected patients with intermediate stage HCC (BCLC stage B) but results have been disputed in several review articles and meta-analyses [62]. TACE can also be performed in smaller tumors unsuitable for ablation because of comorbidity or tumor location. TACE can also be combined with other local ablative approaches in suitable patients and used as a "bridge-to-transplantation" as discussed earlier.

The contraindications to TACE include decompensated cirrhosis, jaundice, encephalopathy, refractory ascites, impaired portal venous flow, extensive bilateral tumor involvement, malignant portal vein thrombosis, large tumor >10 cm, severe comorbidity etc. [62]. Postembolization syndrome may occur after TACE and symptoms include, fever, abdominal pain and nausea and is often self-limited and easily treatable.

SIRT uses the infusion of radioactive substances such as 131-Iodine-labeled Lipiodol or microspheres containing yttrium-90 (Y90) or similar agents to deliver radiation directly to the tumor. Currently, the most popular technique uses resin or glass microspheres coated with Y90, a ß-emitting isotope.

SIRT is performed in a lobar, sectorial, or segmental approach according to tumor size and location. In patients with HCC developed on chronic liver disease, whole-liver treatment in one session is discouraged. Because of the minimal embolic effect of Y90 microspheres, treatment can be safely used in patients with portal vein thrombosis [63]. Compared to TACE, SIRT induces less toxicity, provides significantly longer time to progression and better tumor control and maintains higher quality of life, although it does not provide longer survival [64, 65].

6.5 Systemic Therapy

Sorafenib, is an oral multikinase inhibitor of Raf, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-kit, Flt-3 and RET used for the treatment of patients with advanced HCC (macrovascular invasion/metastatic, BCLC stage C) in patients with good liver function (CTP A and selected CTP B) [4, 44, 66]. Results of the European SHARP trial and an Asia-Pacific trial have shown that Sorafenib prolonged survival (increased median survival by 2–3 months) in patients regardless of age, performance status and extent of the tumor [44, 67]. Sorafenib is usually given at a dose of 400 mg twice a day. Side effects include included diarrhea, fatigue, hand–foot skin reaction and rash/desquamation.

Post the advent of Sorafenib, a number of targeted agents have being evaluated in studies to improve survival with Sorafenib as a comparator arm. Till date, the only other molecule which has been found comparable to sorafenib is Lenvatinib, an inhibitor of VEGF receptors 1-3, FGF receptors 1-4, PDGF receptor α, RET and KIT [68].

Regorafenib is an oral diphenylurea multikinase inhibitor targeting angiogenic stromal and oncogenic receptor tyrosine kinases. It had been approved for the treatment of patients with advanced HCC previously treated with Sorafenib and has been shown to improve survival as compared to placebo [69]. The most common adverse events include fatigue, diarrhea, hypertension and hand–foot skin reaction.

6.6 Immunotherapy

Nivolumab, a fully human IgG4 monoclonal antibody and programmed cell death protein-1 (PD-1) immune checkpoint inhibitor, has been evaluated in a phase I/II open-label, non-comparative, dose escalation and expansion trial (CheckMate 040). Impressive results with Nivolumab resulting in OS of 66% at 6 months and 9 months, and median OS of 15.0 months were seen [70].

The use of systemic chemotherapy with agents like Doxorubicin in the adjuvant setting has not shown any survival advantage and is not recommended [71].

6.7 Stereotactic Body Radiation Therapy (SBRT)

SBRT involves highly precise delivery of high dose of radiation in 3–6 fractions such that it has potential of higher cell kill and ablation of the liver tumor while sparing the normal liver parenchyma. SBRT may be used in patients who have failed other locoregional therapies. It has low toxicity and acceptable local control rates in well-selected patients [72]. It can be used as a stand-alone treatment or in combination with other therapies like TACE and ablation. It may also be used has a bride-to-transplant therapy. Studies are ongoing to further define the role of SBRT in HCC treatment.

6.8 Evaluation of Treatment Response and Follow-Up

HCC if not treated by resection or transplantation responds usually by necrosis to other treatment modalities. This fact forms the basis for the radiological evaluation of treatment effect. The Response Evaluation Criteria in Solid Tumors (RECIST) criteria were subsequently modified by the EASL (mRECIST) and are now considered the gold standard for measuring tumor response during treatment for HCC [73]. Viable tumor is defined as uptake of contrast agent in the arterial phase.

After curative treatment, the initial response evaluation should be performed at 4 weeks. Thereafter, clinical, laboratory and radiologic evaluation using dynamic contrast-enhanced CT or MRI studies every 3 months the first 2 years and thereafter every 6 months is recommended [74]. When recurrence is detected, the patient should be restaged and curative treatment offered if appropriate. Follow-up of HCC patients treated with palliative intention is usually recommended at 3-monthly intervals.

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Gastric Cancer

Manish S. Bhandare and Anant Ramaswamy

Abbreviations

CT	Computerized tomography
DCF	Docetaxel–Cisplatin–5 Fluorouracil
ECX	Epirubicin/Cisplatin/Capecitabine
EGC	Early gastric cancers
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
EUS	Endoscopic ultrasonography
FLOT	Fluorouracil/leucovorin
FOLFIRI	5 Fluorouracil–Irinotecan
GC	Gastric cancer
GEJ	Gastroesophageal junction
JGCA	Japanese Gastric Cancer Association
RFS	Recurrence-free survival

1 Introduction

Gastric cancer (GC) and its management remain an important issue in the world of oncology, owing to a high relapse rate, even after curative treatment. Worldwide, most countries are experiencing a steady decline in the incidence of GC. Contrary to this observation, the projected incidence for India is on increasing trend.

Although a variety of tumors, i.e., adenocarcinoma, lymphoma, carcinoid and sarcoma, are known to occur in stomach, this chapter will focus on gastric adenocarcinomas, which account for more than 90% of all cases of GC.

The reported overall 5-year survival rates for GC are between 20% and 25%, across all stages in most industrialized nations. Stage of disease at time of diagnosis is clearly a single most important factor influencing survival. Patients diagnosed to have earlier stages of gastric cancer have a distinct advantage as against those with higher-stage disease.

2 Epidemiology: Indian and Global Scenario

As is the case for many cancers, the epidemiological distribution of GC demonstrates a marked variation in regional incidence, with as much as a ten-fold difference between the highest- and lowest-risk populations. The highest incidence is found in countries from South East Asia, i.e., Japan, China and South Korea [1]. Globally, India ranks at a much lower level and is considered as a low incidence country. GC in India is counted among the top five common malignancies, being the fifth most common cancer for men while sixth most common for women [2]. The case fatality rate is high, and hence, it is the second most common cause of cancer-related death among patients with malignancy in the age group between 15 and 44 [3, 4].

Unique feature of GC in India is the presence of a wide geographic variation in its incidence. Although only 7% of the population is covered in various registries providing data (NCR-National Cancer Registry, Hospital or population-based registries), the highest incidence in India is recorded from the district of Aizawl from Mizoram state accounting for 62.2/100,000 cases. The state with second most common incidence is Tamil Nadu from South India.

With highest burden of this disease in South East Asia, the annual burden of GC is likely to increase up to 1.8 million new cases and the GC deaths are likely to reach to 1.3 million annually by year 2040.

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3 Risk Factors for Gastric Cancer

Several factors are known to be associated and they may be different depending on the location of the tumor within stomach, e.g., proximal or distal GC. History of gastric dysplasia or adenoma, chronic atrophic gastritis and prior gastric surgery are considered as important risk factors. Irrespective of the geographical region, the worldwide incidence is at least two fold more common in males as compared to females.

For noncardia, i.e., distal or body cancers, chronic infection with *H. pylori* is the commonest risk factor [5]. Alteration of the cell cycle check points and mutations in the tumor suppressor genes related to the *H. pylori* infection are thought to be the prime reasons for carcinogenesis [6]. Dietary habits such as high intake of pickled, smoked, salted, or preserved foods and a low intake of fruits and vegetables may increase the risk of GC [7, 8]. Apart from the dietary factors, tobacco in any form (particularly smoking) is associated with development of GC with predilection of proximal stomach or gastric cardia [9]. Overweight status and obesity are also known to increased GC risk [10]. About 10–15% of cases with GC are associated with familial predilection (5–10%) or inherited syndromes (3–5%) [11]. GC history in a siblings or parent can result in two-fold increased risk [12, 13]. Inherited cancer predisposition syndromes with strongest association for GC are seen in hereditary nonpolyposis colon cancer and hereditary diffuse gastric cancer syndrome (Table 1).

Table 1 Hereditary syndromes with increased risk of developing gastric cancer

Syndrome	Gene(s)	Pattern of inheritance
Hereditary diffuse gastric cancer	CDH1	AD[a]
Lynch syndrome (LS)	EPCAM, MLH1, MSH2, MSH6, PMS2	AD[a]
Juvenile polyposis syndrome (JPS)	SMAD4, BMPR1A	AD[a]
Peutz–Jeghers syndrome (PJS)	STK11	AD[a]
Familial adenomatous polyposis (FAP)/attenuated FAP (AFAP)	APC	AD[a]
Ataxia-telangiectasia	ATM	AR[b]
Bloom syndrome	BLM/RECQL3	AR[b]
Hereditary breast and ovarian cancer syndrome	BRCA1, BRCA2	AD[a]
Li–Fraumeni syndrome	TP53	AD[a]
Xeroderma pigmentosum	7 different genes	AR[b]
Cowden syndrome	PTEN	AD[a]

[a]*AD* autosomal dominant, [b]*AR* autosomal recessive

Apart from the *H. pylori* infection, Epstein–Barr virus infection is also associated with GC development. Its role in carcinogenesis, however, remains unclear [14, 15].

Socioeconomic status, geographical region, Menetrier disease (hypertrophic gastropathy), pernicious anemia and blood group A are the other factors associated with increased risk.

4 Clinical Presentation

In the early stage, often patients do not exhibit any symptoms. Dyspepsia (indigestion, bloating, heartburn, etc.) is often a commonly associated symptom with GC. In more advanced stage, vomiting and nausea, bleeding (hematemesis and/or melena), abdominal pain, lump in epigastric region, unexplained weight loss, loss of appetite and early satiety, can be experienced by the patients. Gastroesophageal junction or proximal gastric tumors can produce dysphagia as an early symptom. Most often, a combination of the above mentioned symptoms are present at the diagnosis.

For advanced, large distal stomach tumors, following signs may be present.

- Lump in the epigastrium.
- Peristalsis can be seen (Left to right) in the left hypochondrium.
- Succussion splash and borborygmi also be noted in obstructing tumors.
- Left supraclavicular adenopathy (Virchow’s node).
- Left axillary node (Irish node).
- Periumbilical nodule (Sister Mary Joseph’s node).
- Ovarian metastasis (Krukenberg’s tumor).
- Mass in the pouch of Douglas on rectal examination (Blumer’s shelf).
- Fluid thrill secondary to ascites.
- Palpable mass in the right hypochondrium (liver metastasis).

5 Evaluation and Work-Up

5.1 Tumor Markers

None of the tumor markers are considered ideal for diagnosis of GC, owing to a low rate of sensitivity and specificity. The serum levels of the following markers may be elevated at presentation [16–18],

- CEA (carcinoembryonic antigen),
- CA 19-9 (carbohydrate antigen 19-9),
- CA 125 antigen (CA 125) and
- CA 72 A (cancer antigen 72-4)

Although the tumor markers are not helpful for diagnosis, if the baseline levels are elevated, their serial rise in the follow-up may be useful to detect disease recurrence [19, 20].

Increases in serum pepsinogen II or decreases in the pepsinogen I: pepsinogen II ratio have been used in population screening programs to identify patients at increased risk for GC but are insufficiently sensitive or specific for establishing a diagnosis in an individual patient.

5.2 Endoscopy

Identification of primary tumor, anatomic localization and tissue diagnosis are best possible by a simple endoscopy (UGI—Upper GI Endoscopy).

During endoscopic assessment, any lesion suspicious for malignancy should undergo biopsy.

Multiple (at least 6–8) biopsies from the lesion are recommended as this increases the diagnostic yield to more than 98% as compared to a single biopsy [21].

5.2.1 Endoscopic Ultrasonography (EUS)

For accurate T staging (knowing the depth of invasion), EUS is the most sensitive investigation [22]. Most benefit is obtained in in detecting T1 lesions. Conventional CT scan techniques could not categorize T stage as reliably as EUS in comparative studies [23, 24]. However, MRI or multidetector 3-D CT scan may perform equally well as EUS to accurately assess T stage [25, 26].

Although EUS has been recommended for pretreatment evaluation in patients without any suspicion of metastatic (M1) disease on conventional CT imaging, in practice it is performed when early GC is suspected on endoscopy and CT scan [1] to identify patients suitable for endoscopic resection or [2] for upfront surgery.

5.3 Pathology

The most commonly used histological classification systems are the Lauren and WHO schemes [27, 28]. As per the Lauren classification, GCs are divided into diffuse and intestinal histological subtypes. Most diffuse GCs are characterized by poor differentiation, have poorly cohesive tumor cells and lack any gland formation. The intestinal types generally are well or moderately differentiated and can form glands. The WHO classification takes into consideration the predominant morphological appearance on histology and has five types, i.e., tubular, papillary, mucinous, poorly cohesive and rare variants. In general, the tubular and papillary types in WHO classification correlates to the intestinal type in the Lauren's classification and have more favorable outcomes, and the poorly cohesive type can be related to the diffuse Lauren's type which has poorer outcome [29].

5.3.1 Molecular Classification

According to the genomic profiling studies by TCGA (The Cancer Genome Atlas) group, four subgroups of primary gastric adenocarcinoma has been identified [30]:

- Positive for Epstein–Barr virus (9%)
- Microsatellite unstable tumors (22%)
- Genomically stable tumors (20%)
- Chromosomally unstable tumors (50%)

Other classifications have also clearly demarcated molecular subgroups with differing clinical characteristics and survival outcomes [31]. Although at present the utility of this classification in the clinical practice is limited, these subtypes may be useful for determining the prognosis more accurately, together with the TNM stage and also lead to developing personalized treatment strategies in future.

5.4 Radiology

A contrast-enhanced computerized tomography (CT) scan is often the initial staging test after confirmation of diagnosis of GC (Figs. 1 and 2). Visceral metastatic disease, e.g., lung, liver, adnexa and distant lymph nodes, can be easily detected on CT scan. Also, it provides information regarding the local extent of the tumor, involvement of adjacent structures (left lobe of liver, pancreatic head, invasion of porta hepatis, etc.) and helps predicting resectability. However, it lacks sensitivity in detecting smaller visceral spread (<5 mm) and peritoneal spread, even using modern CT techniques [32]. PET-CT scan was not considered useful in primary evaluation of GCs as the diffuse type (signet ring cell tumors) lack any FDG activity. However, its role in preoperative evaluation is developing. Integrated PET-CT can be used for knowing the local tumor extent and is more sensitive for detecting metastatic disease [33]. Hence, integrated PET/CT has been suggested in the NCCN guidelines as a part of initial evaluation of GC.

Detection of peritoneal disease still remains a problem, even with the integrated PET-CT, and hence, it cannot substitute staging laparoscopy [34].

5.5 Staging Laparoscopy (SL)

Although SL requires anesthesia and is an invasive surgical procedure to be performed as a part of diagnostic work up, it remains the most sensitive test to detect peritoneal metastasis. Biopsy of any suspicious nodule should be performed during SL along with collection of peritoneal lavage fluid for cytological examination. In patients with radiological T3/T4 tumors without any metastatic spread on imaging, SL upstages the disease which leads to change in management plan in about 20–30% cases [35, 36]. Hence, SL is a part of

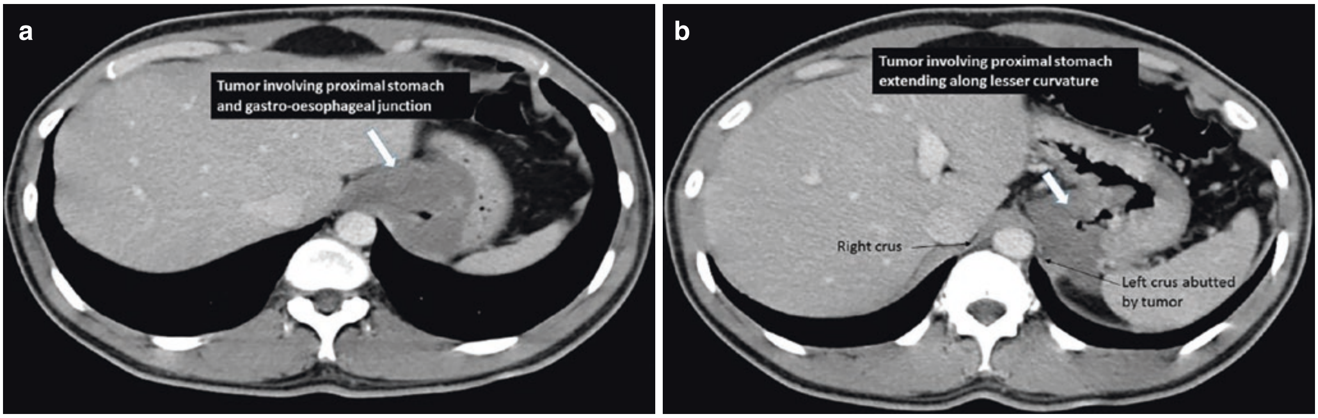

a
Tumor involving proximal stomach and gastro-oesophageal junction
b
Tumor involving proximal stomach extending along lesser curvature
Right crus
Left crus abutted by tumor

Fig. 1 (**a**, **b**) Contrast-enhanced CT scan: proximal gastric cancer

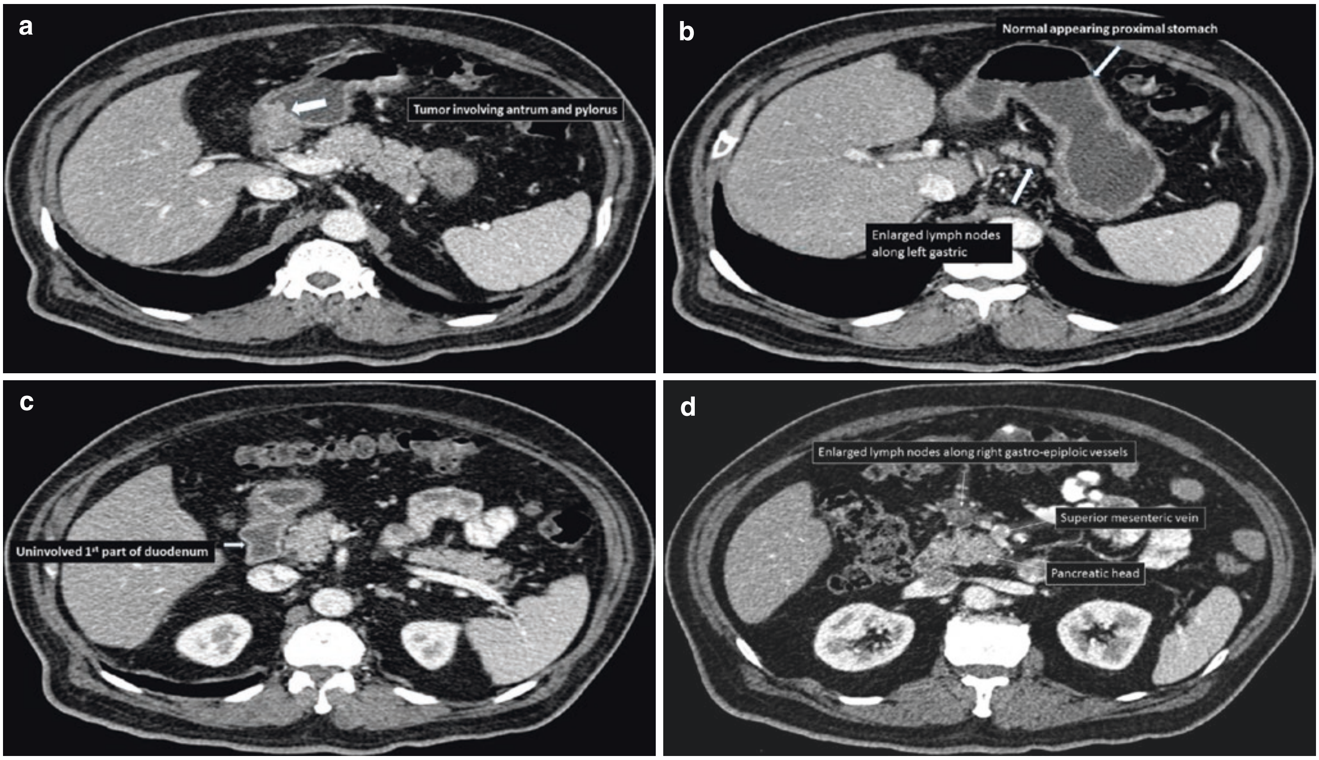

a
Tumor involving antrum and pylorus
b
Normal appearing proximal stomach
Enlarged lymph nodes along left gastric
c
Uninvolved 1st part of duodenum
d
Enlarged lymph nodes along right gastro-epiploic vessels
Superior mesenteric vein
Pancreatic head

Fig. 2 (**a–d**) Contrast-enhanced CT scan: distal gastric cancer

routine evaluation for all patients with locoregionally advanced disease (cT3/T4, N+ disease).

5.6 Referrals Including Genetic Counseling

As discussed previously, about 5–10% GCs have a familial association and about 3–5% are a part of inherited cancer syndrome.

Genetic counseling or testing is recommended in the following situations [37]:

- Existing GC gene mutation in the family
- GC in one family member at a young age (< 40 years of age), or
- GC in 2 first/second-degree relatives with one diagnosis before age 50, or
- GC in 3 first/second-degree relatives independent of age, or
- GC and breast cancer in one patient with one diagnosis before age 50, or
- GC in one patient and breast cancer in one first/second-degree relative with one diagnosis before age 50

The malignancy risk assessment during genetic counseling should include a complete family history of all medical and surgical treatments. A detailed and focused physical examination should be performed along with psychosocial assessment. Also, the available mental and financial support in the event of a problem should be assessed. Following which an informed consent is obtained and necessary genetic tests are ordered.

6 Principles of Management

The management of GC requires a multidisciplinary approach. All patients are staged according to the AJCC classification [38]. Once clinical staging is complete, appropriate treatment plan is established in the multidisciplinary clinic and is often with curative intent for patients with stage I, II and III disease, while the approach is palliative for most cases with stage IV disease.

Radical surgery remains at the cornerstone in the management of GC. Neoadjuvant chemotherapy (perioperative chemotherapy) has an established role in patients with locoregional disease and is considered as standard of care outside South East Asia. Postoperative chemotherapy or postoperative chemo radiation, are alternative approaches for these tumors.

GC can be categorized into following groups for describing various treatment approaches,

6.1 Early Gastric Cancers (EGC) [T1a/T1b N0/N+ M0]

EGC is defined as cancer which is confined to the mucosa and submucosa regardless of lymph nodes status. Following are treatment options depending on the lesion characteristics, presence of LN status and availability of expertise:

- Endoscopic resection [39]: endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD).
- Surgery (radical gastrectomy/local resection) [40, 41].
- Antibiotic treatment for eradication of *Helicobacter pylori* [42].
- Adjuvant chemotherapy for patients with N+ disease.

6.2 Gastric Cancer with Locoregional Disease [T2-T4 N+ M0]

Treatment strategies are:

- Perioperative chemotherapy with radical D2 gastrectomy (as per MAGIC protocol) [43].
- Radical D2 gastrectomy followed by adjuvant chemoradiotherapy [44–46].
- Radical D2 gastrectomy with adjuvant chemotherapy [47, 48].

6.3 Advanced Gastric Cancers [Unresectable T4 N+ or M1]

Depending on the overall health and performance status of the patient, following are options:

- Surgery: Palliative gastrojejunostomy, palliative gastrectomy (highly selected cases with gastric outlet obstruction or persistent tumor bleed unresponsive to other mode of bleeding control).
- Palliative chemotherapy: With intent of improving QOL and survival.
- Palliative radiotherapy: For pain control and for controlling chronic/slow tumor bleed.
- Symptomatic palliation of pain and ascites.

7 Surgical Management

The aim of surgery for GC surgery is to obtain a complete tumor removal with adequate margins. The involved part of the stomach is removed resecting approximately 5 cm of normal appearing, healthy stomach proximal as well as distal to the tumor. This 5 cm margin is not possible distally in antropyloric tumors and proximally for GE junction or cardia tumors. At these instances, a 1 cm margin at duodenum or esophagus respectively, is acceptable. However, it should always be confirmed on intraoperative frozen section. The standard lymph node clearance should be D2 dissection. As per the tumor location within stomach; distal subtotal, proximal or total gastrectomy are accepted as oncologically sound procedures (Fig. 3).

- Total gastrectomy: It is performed for tumors involving entire stomach (linitis plastica) or body tumors with involvement of lesser curvature (proximal to incisura) or large/bulky proximal tumors with significant peri gastric lymph node involvement.
- Distal subtotal gastrectomy: Performed for tumors involving antrum-pylorus, distal body and tumors not extending proximal to incisura.
- Proximal gastrectomy: Is an option for early stage tumors of the cardia, proximal body without significant perigastric lymphadenopathy.

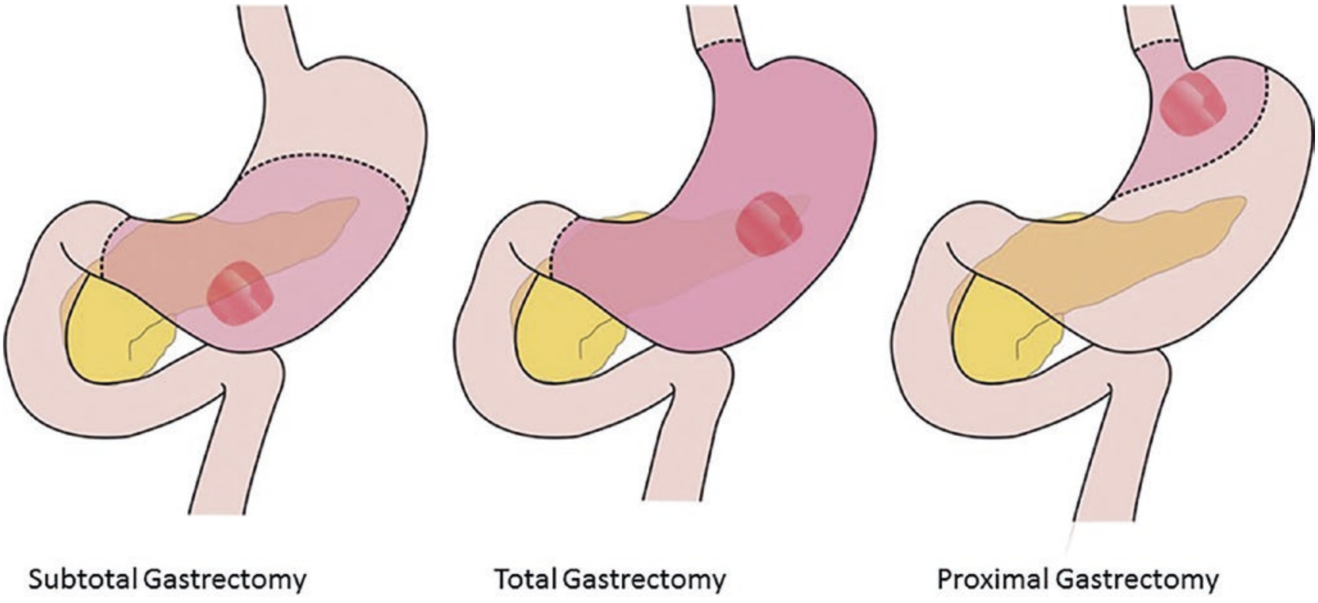


Fig. 3 Types of radical gastrectomy

7.1 Surgery for Distal Tumors

For tumors involving distal part of the stomach, the available evidence comparing distal subtotal vs. total gastric resection did not show any survival difference [49, 50]. The advantage with a more conservative distal subtotal gastrectomy is to offer a better QOL, maintenance of nutritional status and weight as compared to total gastrectomy and hence is the standard of care for tumors in this location.

7.2 Surgery for Proximal Tumors

According to the Japanese Gastric Cancer Treatment Guidelines (2010), both proximal and total gastrectomy can be options for early-stage disease involving the cardia or proximal body [51]. In general, proximal gastrectomy should be avoided in more advanced tumors with regional lymphadenopathy as D2 dissection is not possible with proximal alone resections. However, the available evidence is not robust, and some reposts mention feasibility and oncological safety of this procedure even in locally advanced proximal GCs after neoadjuvant chemotherapy (NACT), when it is technically feasible [52]. Still, a total gastrectomy is favored for the following reasons:

- Biliary reflux causing esophagitis and later stricture can be a known complication with proximal gastrectomy; however, it is never a problem with the Roux-n-Y anastomosis performed during the total gastrectomy [53].
- Perigastric lymph node stations, namely station 4, 5 and 6 are left behind during proximal gastrectomy and can compromise oncological safety.

7.3 Surgery for Early Gastric Cancer (EGC)

EGC was first defined in 1962 by the Japanese Society of Gastroenterological Endoscopy as adenocarcinoma confined to the mucosa or submucosa irrespective of lymph node involvement [54]. The incidence of EGC remains extremely low outside South East Asia, as dedicated screening programs are not available. With tumors meeting certain endoscopic criteria, endoscopic resection is an option. Surgical resection still remains a commonly used approach for EGC and is associated with 5-year survival rate of up to 98% [40, 41]. If the expertise for EMR/ESD is not available, limited surgery with wide local resection is an option in suitable cases.

For tumors limited to mucosa, lymph node involvement rate is very low and is ≤3%, whereas the risk of nodal metastasis is 15–20% when the submucosa is involved. Thus, local resections can be offered in diseases confined to mucosa and a radical gastrectomy with lymphadenectomy is performed for diseases involving submucosa [55]. The role of sentinel lymph node mapping in EGCs is still considered investigational [56].

Laparoscopic radical gastrectomy (particularly distal subtotal resections) for relatively early stage gastric cancer offers short-term benefits in terms of reduced blood loss, pain and hospital stay in the postoperative period and is oncologically equivalent to open approach [57–59].

7.4 Role of Bursectomy During Radical Gastrectomy

Until recently, the role of routine bursectomy was debatable during gastric resections for cancer. Bursectomy has been recommended selectively by the Japanese guidelines for T4 or serosa involving tumors only as routine use may be harmful by causing pancreatic or vascular injuries during dissection. In 2014, a meta-analysis including two RCTs and three retrospective studies could not find any survival advantage with bursectomy as compared to nonbursectomy [60]. Patients with disease involving serosa showed a trend toward an improved OS with bursectomy; although the difference was not statistically significant. In 2018, a large RCT (JCOG1001) from Japan included over 1200 patients. The aim was to evaluate the benefit of bursectomy in gastric cancer. Nearly 80% of the included patients had cT3/T4a disease, and about 70% were node positive. The long-term results showed comparable 5-year OS rate (76%) in the bursectomy and nonbursectomy arm. Although bursectomy was safe, the authors did not recommend it routinely for cT3 or cT4a GC [61].

7.5 Lymphadenectomy During Radical Gastrectomy

The Japanese Gastric Cancer Association (JGCA) classifies the lymph node stations as well as the extent of lymph node dissection performed for gastric cancer. The extent of lymph node dissection is classified as D1, D2, D3 and D4 [51, 62]. D1 comprises dissection of station 1–6, D2 involves removal of D1 along with station 7–11 (Fig. 4), D3 takes in removal of D2 with station 12–14 (Fig. 5) and D4 means dissection of D3 with station 15–16.

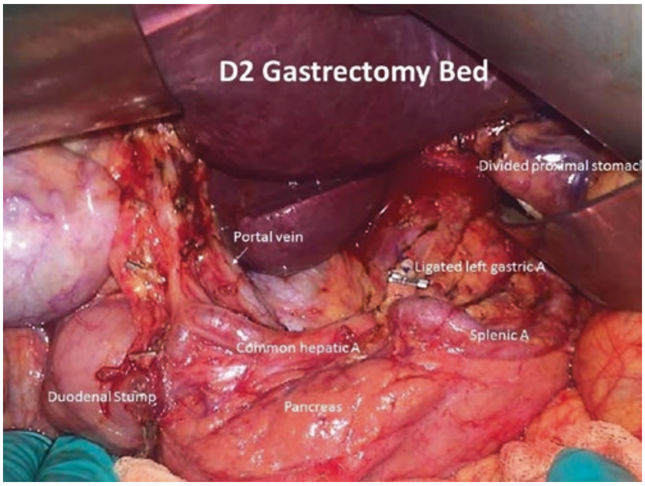


Fig. 4 Intraoperative image, post D2 lymph node dissection

D2 lymphadenectomy remains a standard practice in Japan since the 1960s. However, because of lack of survival benefit and higher postoperative morbidity shown in the initial results of the Dutch trial, D2 dissection did not gain popularity in the western world [63, 64]. A retrospective study from Tata Memorial Hospital suggests that morbidity and mortality following D2 lymphadenectomy (spleen preserving) is low, i.e., 8.8% and 1.25% [65].

A randomized controlled trial from Taiwan showed an overall survival (OS) and recurrence-free survival (RFS) benefit for a D2/D3 dissection as compared with D1 lymphadenectomy, without any added perioperative mortality [66].

Later, the 15-year follow-up of the Dutch Trial showed gastric cancer-specific deaths were less in the patients undergoing D2 dissection and the difference was statistically significant [67]. When the perioperative mortalities were excluded, the benefit of D2 was further amplified. As per the protocol of the trial, the standard D2 dissection at that time included routine performance of distal pancreaticosplenectomy which could have been the reason for higher perioperative morbidity/mortality with D2 surgery. With these results, the authors concluded and recommended spleen/pancreas preserving D2 dissection as a standard of care for patients with resectable gastric cancer.

In 2013, a meta-analysis that included 12 RCTs on various lymphadenectomies performed for gastric cancer resection did not find any survival benefit with D2 compared to D1 lymphadenectomy. But, similar to the long-term follow-up data of the Dutch trial, a subgroup analysis of patients undergoing spleen/pancreas preserving D2 dissection showed a trend for improved OS [68]. Additionally, the RFS was significantly better with D2 dissection. Only one trial in the meta-analysis evaluated D3 dissection and did not find any benefit as compared to D2 dissection.

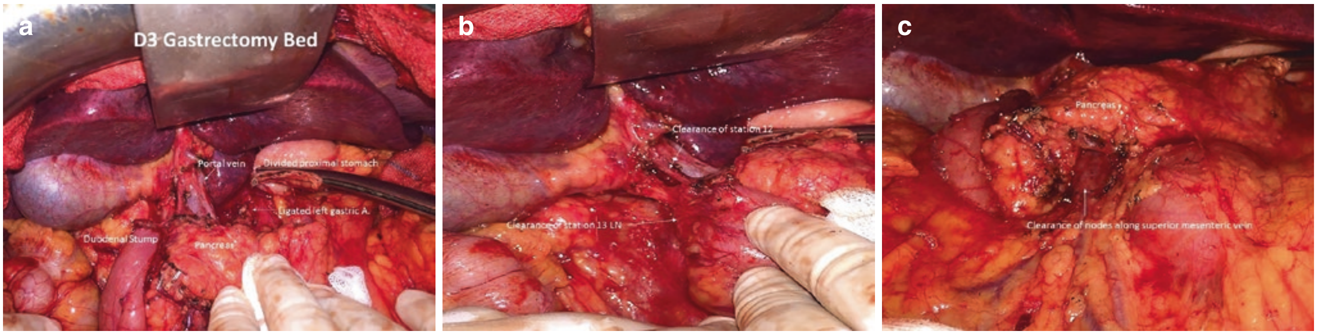


Fig. 5 (a–c) Intraoperative image, post D3 lymph node dissection

An ongoing “Phase III Randomized Trial Comparing D2 vs. D3 Lymphadenectomy with Gastric Cancer Following Neoadjuvant Chemotherapy” (ELANCe trial, clinicaltrials.gov trial ID—NCT02139605) is evaluating the role of D3 dissection for resectable gastric cancer after neoadjuvant chemotherapy [69].

To summarize, the present surgical standard of care remains a spleen preserving D2 dissection for all resectable gastric cancers excluding few early gastric cancers where lesser resection is possible. Distal pancreaticosplenectomy is no longer recommended as a routine practice with D2 dissection. At present a minimum of 16 nodes should be evaluated at histological examination to qualify for an adequate D2 dissection. Laparoscopic surgery is possible and has shown oncologically equivalent results when performed in high volume centers.

8 Medical Management

8.1 General Principles

The management of gastric cancer from a medical oncologist perspective depends on the stage of the primary disease as well as the institutional treatment protocol. All stages of gastric cancer beyond stage 1A tumors require an assessment by the medical oncology unit. For patients with Tis or T1, N0 disease who have uninvolved resection margins, observation is recommended. Adjuvant therapy is recommended for all patients with lymph node-positive disease, regardless of T stage.

The management and survival outcomes of LA-GC (T3/T4 N+ disease) have been markedly improved with the introduction of perioperative therapy. Based on multiple well-conducted Phase III trials, perioperative therapy is the present standard of care for patients with LA-GC. However, due to global variations in presentation and the differences in treatment strategies between the “West” (US, Western Europe) and “East”(Japan, South Korea, China), the standardized approach is yet to be defined. Recommended approaches to the treatment of LA-GC include perioperative chemotherapy and adjuvant therapy.

8.2 Perioperative Chemotherapy

The combination of neoadjuvant therapy, followed by radical surgery and adjuvant chemotherapy is primarily used in European countries and is practiced as per the results of the pivotal MAGIC trial as well as a later FNCLCC/FFCD study (albeit, having only 25% GC patients and analyzed early as a result of accrual issues) [43, 70]. The benefits of using neoadjuvant chemotherapy include tumor downstaging and thus improving R0 resections, micrometastases elimination, improving symptoms (tumor-related) and an assessment of tumor biology. While the MAGIC trial used the Epirubicin–5 Fluorouracil–Cisplatin (ECF), the French study used Cisplatin–5 Fluorouracil (CF) as their regimen of choice. Although there were some differences in the populations selected for the two trials in terms of baseline clinical characteristics, the benefits of perioperative chemotherapy in both trials were of a similar nature, being 13% and 14% (5-year mOS benefit) over surgery alone, respectively. Though ECF/CF have been shown effective in Phase III clinical trials, the ECF regimen used in the MAGIC trial was an infusional protocol requiring a central line (9 weeks over 3 cycles) which may not be feasible across clinical practice settings. As an alternative to this regimen, Epirubicin–Oxaliplatin–Capecitabine (EOX),, Epirubicin–Oxaliplatin–5 Fluorouracil (EOF) and Epirubicin–Cisplatin–Capecitabine (ECX) are acceptable regimens that can be used as neoadjuvant therapy. This is based on the near equivalence of these regimens in the locally advanced/metastatic setting and extrapolation of data to the perioperative setting. A large retrospective study from TMH has shown the feasibility of using EOX regimen as perioperative therapy in GC with outcomes on par with published data [71]. The benefit of a third drug, Epirubicin, over a cisplatin-5-Fluorouracil regimen of neoadjuvant chemotherapy was explored in the UK MRC OEO5 trial, which compared ECX with CF in locally advanced esophageal adenocarcinomas. While some benefit was observed in disease-free survival (DFS) and tumor regression, there was no benefit in OS, throwing into question the potential additional benefit of Epirubicin in the perioperative setting [72]. Further evidence of lack of benefit of an epirubicin-based regimen comes from the FLOT4-AIO trial, which evaluated perioperative chemotherapy with docetaxel, oxaliplatin and fluorouracil/leucovorin (FLOT) versus ECF/ECX for resectable gastric or gastroesophageal junction (GEJ) adenocarcinomas. There was clinically and statistically significant improvement in median PFS (18 months with ECX/ECF vs. 30 months with FLOT; p = 0.004) as well as median OS (35 months with ECX/ECF vs. 50 months with FLOT; p = 0.012) with the FLOT arm, thereby suggesting that FLOT should be current standard of care as perioperative therapy [73].

8.3 Adjuvant Therapy

Upfront surgery followed by adjuvant chemotherapy is the current standard practice in centers from South East Asia treating gastric cancers in high volumes. This standard has been established based on well conducted Phase III trials, including older trials like INT-116 and newer studies such as

ACTS-GC, CLASSIC and ARTIST, which examined the role of adjuvant therapy after a D2 Gastric resection [44, 45, 47, 48]. There have been at least four meta-analyses of adjuvant therapy trials which have confirmed survival benefit of adjuvant therapy as against surgery alone in this subset of patients, and hence, adjuvant therapy is the current standard in patients undergoing upfront D2 Gastric resections [46, 74, 75]. While "adjuvant therapy" is standard, there exists some debate over chemotherapy alone vs. chemoradiation as the appropriate adjuvant therapy. Beyond INT-116, which essentially had a small proportion of D2 resections (approximately 10%), high incidences of acute toxicity as well as outdated radiotherapy techniques and no chemotherapy-only arm, the study in the current era which was best positioned to answer this debate was the well planned ARTIST trial [44, 45]. The updated analysis after a median 7-year follow-up comparing chemotherapy (Capecitabine–Cisplatin for alone cycles) vs. chemoradiation (Capecitabine–Cisplatin for two cycles, followed by chemoradiotherapy and further Capecitabine–Cisplatin for two cycles), in an intention to treat analysis, showed no difference between the arms in terms of median DFS or median OS. However, an unplanned subset analysis suggested OS benefit in patients with diffuse type GC and node-positive disease. Additional caveats regarding the role of chemotherapy alone vs. chemoradiation are elucidated in two large meta-analyses evaluating the two modalities, which showed an improvement with chemoradiation in DFS and loco regional recurrence-free survival, but no improvement in OS [76, 77]. In areas where expertise for D2 resections does not exist, chemoradiation can be considered as adjuvant therapy as opposed to chemotherapy alone.

9 Radiotherapy

9.1 Neoadjuvant Chemoradiation

The remarkable improvement in outcomes seen with neoadjuvant chemoradiation and surgery vs. surgery alone in resectable esophageal cancers has not been translated into routine use in gastric cancers [78, 79]. While there is a well-designed phase II/III trial (TOPGEAR) evaluating such an approach in esophagogastric and gastric adenocarcinomas ongoing, such an approach should only be considered within a trial setting [80].

9.2 Adjuvant Chemoradiation

The combination of improved surgical techniques, greater emphasis on D2 gastric resections as standard as well as improvement in systemic chemotherapy have lessened the role of adjuvant chemoradiation in R0 resected gastric cancers, though controversy still exists on certain aspects. While the seminal INT116 study was the first study which showed improved outcomes with adjuvant chemoradiation, more recent data has raised questions on the benefit of adjuvant chemoradiation as opposed to adjuvant chemotherapy alone [44, 81]. Certain aspects of this contentious issue have been covered previously.

Beyond the previously discussed ARTIST study in which patients who underwent upfront surgery were randomized, another aspect of adjuvant therapy is the role of adjuvant chemoradiation after surgery following neoadjuvant chemotherapy. This precise question was evaluated by the phase III RCT (CRITICS trial), which evaluated patients with stage Ib–IVa resectable gastric cancer. Both arms received neoadjuvant chemotherapy with 3 courses of ECX or EOX. Post radical gastrectomy, adjuvant therapy was either 3 courses of ECX/EOX or concurrent chemoradiation (45 Gy in 25 fractions combined with weekly cisplatin and daily capecitabine) [82]. The 5-year OS was not different between both arms (41.3% vs. 40.9%; $p = 0.99$). However, in R1 resections, there appears to be a benefit for adjuvant chemoradiation as compared to observation alone, though observation would not be considered standard in resected gastric cancers beyond stage IB in the current era [83].

9.3 Radiotherapy Protocol

The minimum standard that should be employed in the adjuvant potentially curative setting should be three dimensional CT-based planning. The target volume should include the primary tumor or resection bed, gastric remnant (after partial or subtotal gastrectomy) and regional lymph nodes. The inclusion of surgical anastomosis or the divided first part of duodenum may be considered in certain settings. The standard dose in the adjuvant setting includes 45 Gy given in 25 daily fractions. In case of a gross residual disease or for a positive surgical margin, a boost of 5.4–9 Gy may be given [84].

10 Medical Management of Advanced Inoperable/Metastatic Gastric Cancers

The treatment of AGC comprises of continued supportive care as well as chemotherapy and rarely, radiotherapy and surgery. While these patients are treated with "palliative" noncurative intent, it is incumbent on the treating physician to ensure maximum symptom palliative as well as appropriate systemic chemotherapy. A certain proportion of patients will probably benefit maximally from supportive care only.

Patients on palliative chemotherapy for advanced gastric cancers also benefit from referral for early palliative care as an ongoing process [85].

The chemotherapeutic basis for the management of AGC revolves around a 5 Fluorouracil/Platinum doublet, with varying modifications of this combination as well as addition of a third agent, i.e., docetaxel and epirubicin, improving response rates and potentially, survival.

Based on the REAL study and ML17032 studies, an Epirubicin–5 Fluorouracil/Capecitabine-Cisplatin/Oxaliplatin triplet is a regimen of choice in patients with overall good general condition (good ECOG/PS) and possibility of timely visits in the clinic to assess toxicity [86]. A Docetaxel–Cisplatin–5 Fluorouracil (DCF) triplet combination is also associated with good response rates and mOS, although with high rate of Grade 3 and Grade 4 toxicity. An mDCF regimen (with reduced Docetaxel and cisplatin doses) has been associated with improved survival and tolerability as compared to the classical DCF regimen [87]. A variation of this triplet is the Docetaxel–Oxaliplatin–Capecitabine combination, which is widely used and builds upon the marginally better outcomes associated with Capecitabine when compared to 5 Fluorouracil and Oxaliplatin [88, 89].

When triplet combination is not feasible, a doublet Cisplatin/Oxaliplatin–5 FU/Capecitabine is an acceptable regimen. Despite the superior response rates and marginally improved survival associated with a triplet, a well conducted Phase III French trial actually showed no difference in median PFS and OS between FOLFIRI (5 Fluorouracil–Irinotecan) and ECX (Epirubicin/Cisplatin/Capecitabine) [90].

As opposed to combination regimens, single-agent Docetaxel, Paclitaxel and Capecitabine have also shown feasibility and can be used as palliative chemotherapy.

While chemotherapy remains the backbone of therapy for AGC, HER2-neu-positive AGC has the additional option of adding Trastuzumab to a 5 FU–Platinum doublet as per the results of the TOGA trial [91]. No other anti-HER2 neu-directed therapy has shown benefit over conventional chemotherapy. The use of other targeted agents such as bevacizumab and ramucirumab has not shown statistical or clinically significant benefits in combination chemotherapy as opposed to chemotherapy alone in the first-line therapy [92–94].

In patients with progression or recurrence after initial first-line therapy, but with adequate organ function and ECOG PS, recommended second-line agents include Paclitaxel, Docetaxel, Irinotecan and Ramucirumab (as monotherapy or in combination with paclitaxel) [95–97]. All these agents have proven modest but statistically significant survival benefit over best supportive care only with improvement in QOL as well. FOLFIRI combination chemotherapy can also be considered as an appropriate second-line regimen in fit patients [98]. While the above mentioned drugs are recommended in the second-line settings, a review of the cost benefit ratio as well as expectedly modest benefits should be discussed while planning therapy for individual patients [99].

10.1 Immunotherapy

The approval of pembrolizumab in patients with tumors showing microsatellite instability (MSI-H) is a first for any kind of therapy in terms of being a tumor agnostic marker [100]. Pembrolizumab and nivolumab have both been evaluated in advanced gastric cancers post two lines of therapy with modest benefits, making them feasible options in such a setting [101, 102].

11 Stage-Wise Survival of Gastric Cancer

The last two decades have witnessed an improvement in survival for patients with gastric cancer; across stages, based on a combination of improved surgical techniques, systemic chemotherapy, the advent of targeted therapy as well as better supportive care. Such an improvement has been noted in trials as well as in population-based data. However, there is a vast disparity in survival across population, the premier example of which is the improved difference in survival seen across stages in patients treated in South East Asia as opposed to Europe and North America. The improved survivals seen in south-east Asia has been considered related to screening programs, possible earlier diagnosis, different pathological staging, different biology and differential expertise and uptake of D2 resections [103–105]. Based on available data from the National Cancer Database survival data, a rough guide to expected 5-year survival as per stage is presented in Table 2 with data for stage IV cancers as per available trial data [106].

Table 2 Stage-wise survival for gastric cancer

Stage	5-year overall survival (%)
I	88–94
II	68–82
III	18–54
IV	5–15

12 How We Do It at TMC

Figures 6 and 7 present suggested treatment algorithms based on the multidisciplinary approach used in Tata Memorial Hospital.

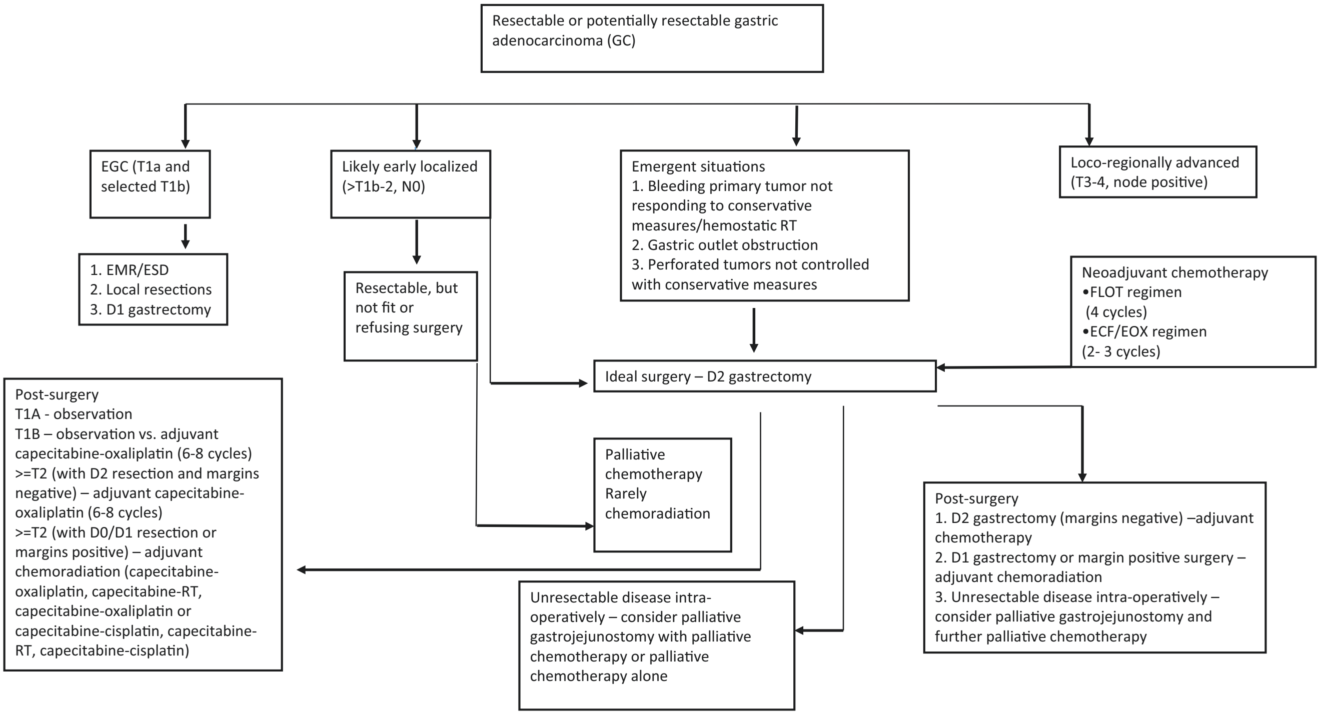
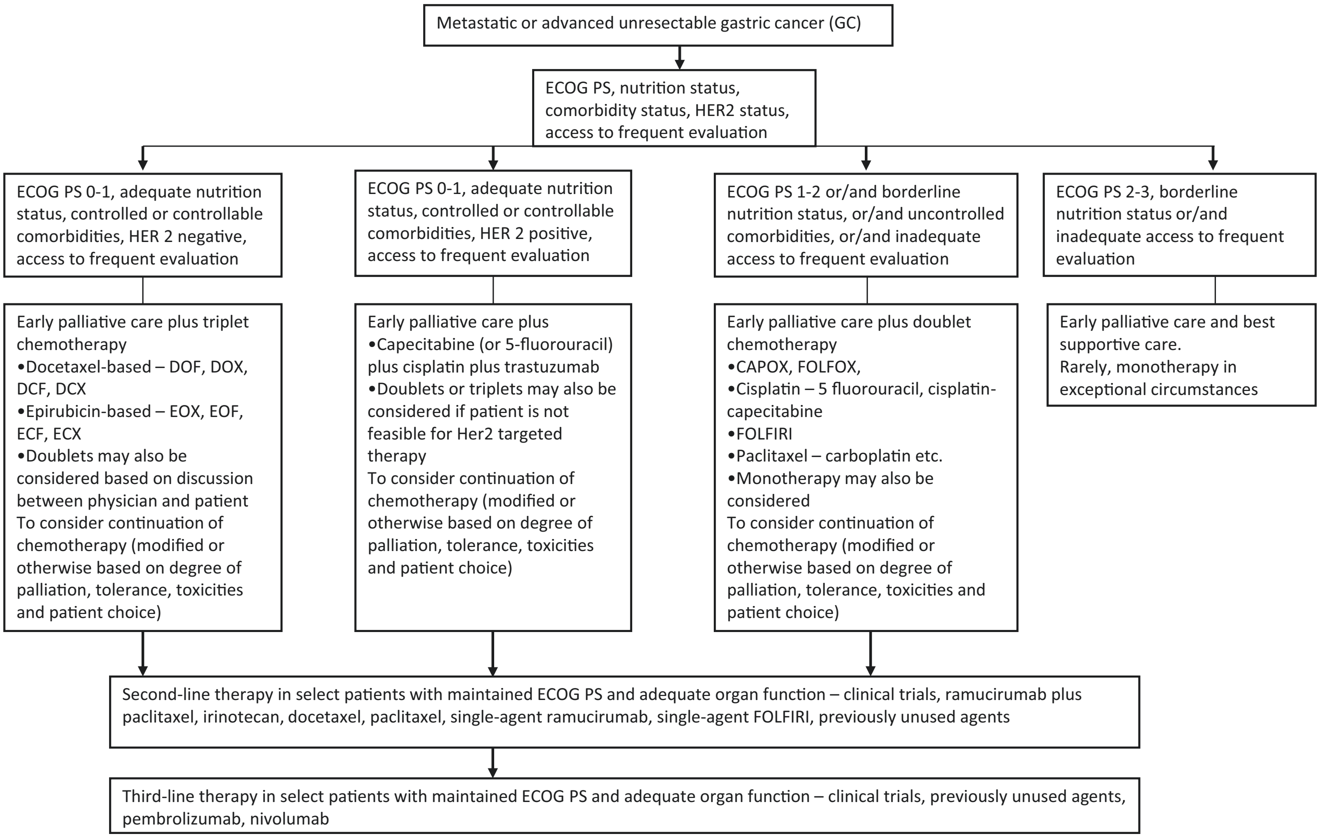

Resectable or potentially resectable gastric adenocarcinoma (GC)
EGC (T1a and selected T1b)
1. EMR/ESD
2. Local resections
3. D1 gastrectomy
Likely early localized (>T1b-2, N0)
Resectable, but not fit or refusing surgery
Emergent situations
1. Bleeding primary tumor not responding to conservative measures/hemostatic RT
2. Gastric outlet obstruction
3. Perforated tumors not controlled with conservative measures
Loco-regionally advanced (T3-4, node positive)
Neoadjuvant chemotherapy
•FLOT regimen (4 cycles)
•ECF/EOX regimen (2- 3 cycles)
Ideal surgery – D2 gastrectomy
Post-surgery
T1A - observation
T1B – observation vs. adjuvant capecitabine-oxaliplatin (6-8 cycles)
>=T2 (with D2 resection and margins negative) – adjuvant capecitabine-oxaliplatin (6-8 cycles)
>=T2 (with D0/D1 resection or margins positive) – adjuvant chemoradiation (capecitabine-oxaliplatin, capecitabine-RT, capecitabine-oxaliplatin or capecitabine-cisplatin, capecitabine-RT, capecitabine-cisplatin)
Palliative chemotherapy Rarely chemoradiation
Unresectable disease intra-operatively – consider palliative gastrojejunostomy with palliative chemotherapy or palliative chemotherapy alone
Post-surgery
1. D2 gastrectomy (margins negative) –adjuvant chemotherapy
2. D1 gastrectomy or margin positive surgery – adjuvant chemoradiation
3. Unresectable disease intra-operatively – consider palliative gastrojejunostomy and further palliative chemotherapy

Fig. 6 Treatment algorithm for localized/resectable GC



Metastatic or advanced unresectable gastric cancer (GC)

ECOG PS, nutrition status, comorbidity status, HER2 status, access to frequent evaluation

ECOG PS 0-1, adequate nutrition status, controlled or controllable comorbidities, HER 2 negative, access to frequent evaluation

Early palliative care plus triplet chemotherapy
•Docetaxel-based – DOF, DOX, DCF, DCX
•Epirubicin-based – EOX, EOF, ECF, ECX
•Doublets may also be considered based on discussion between physician and patient
To consider continuation of chemotherapy (modified or otherwise based on degree of palliation, tolerance, toxicities and patient choice)

ECOG PS 0-1, adequate nutrition status, controlled or controllable comorbidities, HER 2 positive, access to frequent evaluation

Early palliative care plus
•Capecitabine (or 5-fluorouracil) plus cisplatin plus trastuzumab
•Doublets or triplets may also be considered if patient is not feasible for Her2 targeted therapy
To consider continuation of chemotherapy (modified or otherwise based on degree of palliation, tolerance, toxicities and patient choice)

ECOG PS 1-2 or/and borderline nutrition status, or/and uncontrolled comorbidities, or/and inadequate access to frequent evaluation

Early palliative care plus doublet chemotherapy
•CAPOX, FOLFOX,
•Cisplatin – 5 fluorouracil, cisplatin-capecitabine
•FOLFIRI
•Paclitaxel – carboplatin etc.
•Monotherapy may also be considered
To consider continuation of chemotherapy (modified or otherwise based on degree of palliation, tolerance, toxicities and patient choice)

ECOG PS 2-3, borderline nutrition status or/and inadequate access to frequent evaluation

Early palliative care and best supportive care.
Rarely, monotherapy in exceptional circumstances

Second-line therapy in select patients with maintained ECOG PS and adequate organ function – clinical trials, ramucirumab plus paclitaxel, irinotecan, docetaxel, paclitaxel, single-agent ramucirumab, single-agent FOLFIRI, previously unused agents

Third-line therapy in select patients with maintained ECOG PS and adequate organ function – clinical trials, previously unused agents, pembrolizumab, nivolumab

Fig. 7 Treatment algorithm for metastatic/unresectable GC

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Colon Cancer

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> *Cancer is a word, not a sentence.*
>
> *Rob Buckman*

> *There is tremendous literature on cancer, but what we know for sure about it can be printed on a calling card.*
>
> *August Bier*

Abbreviations

CEA	Carcinoembryonic antigen
CECT	Contrast-enhanced computed tomography
CHRPE	Congenital hypertrophic retinal pigment epithelium
CME	Complete mesocolic excision
COST	Clinical Outcomes of Surgical Therapy Study Group
CRC	Colorectal cancer
CRM	Circumferential radial margin
CRS	Cytoreductive surgery
CTC	CT colonography
DCBE	Double-contrast barium enema
EGFR	Epidermal growth factor receptor
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
FAP	Familial adenomatous polyposis
FIT	Fecal immunochemical test
FOBT	Fecal occult blood test
HDI	Human development index
HIPEC	Heated intraperitoneal chemotherapy
HNPCC	Hereditary nonpolyposis colorectal cancer
LR	Local recurrence
MOSAIC	Multicenter International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer Trial
NBI	Narrow-band imaging
OS	Overall survival
QOL	Quality of life
RR	Recurrence rate
TME	Total mesorectal excision
TPA	Tissue polypeptide antigen
TPS	Tissue polypeptide-specific antigen
VEGF	Vascular endothelial growth factor

1 Introduction

Colorectal cancer is one of the most common cancers encountered in clinical practice worldwide. Over 1.8 million new colorectal cancer cases and 881,000 deaths are estimated to occur in 2018, and it ranks third in terms of incidence but second in terms of mortality. It is the third most common cancer in men and second in women [1] Traditionally, colorectal cancer has been recognized as a malignancy of the developed world with the highest incidence rates reported in parts of Europe, Australia, New Zealand, North America, and East Asia and the lowest rates in Africa and Southern Asia. However, recent statistics suggest a declining trend in the developed world which has been attributed largely to the adoption of best practices in cancer

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treatment including screening and efforts directed towards early detection [1]. On the other hand, with increasing urbanization, economic development, growing westernization, and an increasing human development index (HDI), a sharp increase in the incidence has been noted in the developing world [1]. Surgery forms the mainstay in the curative treatment of colon cancer. However, modern polyagent chemotherapy, targeted therapy, and the newly introduced immunotherapy significantly improve survival outcomes in the advanced and metastatic stages of the disease. This chapter deals with colon cancer, its pathogenesis, prognosis, and current standards of care.

2 Incidence and Epidemiology in India and the World

2.1 Incidence

The incidence of colorectal cancer (CRC) demonstrates significant geographic variation. In India, colon cancer ranks ninth among the most common cancers in men and women vis-à-vis the western world where it constitutes the third most common cancer in men and the second most common in women [1].

2.2 World Trends

For both sexes combined, lung cancer is the most commonly diagnosed cancer (11.6% of all cases) and the leading cause of cancer deaths (18.4% of all cancer deaths) closely followed by female breast cancer (11.6%) and colorectal cancer (10.2%). Overall, colorectal cancer ranks third in terms of incidence but second in terms of mortality [1] The annual age-standardized incidence rate in the United States for colorectal cancer from 2009 through 2013, was 40.7 per 100,000 persons with a mortality rate of 14.8 per 100,000 persons [2] Although incidence and mortality rates are higher in men than women, the lifetime risk of the disease is similar owing to the longer female life expectancy. The socioeconomic disparity in the incidence of colorectal cancer is attributed to an unequal prevalence of risk factors such as obesity, unhealthy diet, and smoking [3].

2.3 Domestic Trends

There is very little variation in the incidence rates of CRC across India, unlike the striking regional differences in the incidence rates of stomach and gall bladder cancer. Population-based time-trend studies show a rising trend in the incidence of CRC in India. Indian immigrants to the United Kingdom and the USA have higher incidence rates of CRC as compared to their Indian counterparts, suggesting that lifestyles and dietary habits probably have some causative influence. This also suggests that as India transitions from a low to a middle-income economy, there will be a substantial increase in the burden of colorectal cancer [4] The absolute burden of CRC has also increased in India during the last three decades. During a 32-year period (1941–1972), 555 cases of CRC were recorded at the Tata Memorial Hospital, Mumbai [5]. In contrast, a total of 560 cases of CRC were treated at the same institution in 2006 alone. Age-adjusted colon cancer incidence rates for the world standard population per 100,000 persons in India are 4.3 for males and 3.4 for females [4].

Colorectal cancer in India tends to present at a younger age, at a more advanced stage, with a higher incidence of signet-ring morphology, and more likely to arise in the anorectum vis-à-vis colon [6–11] A study conducted at the Tata memorial hospital, Mumbai confirmed the above findings where the mean age of patients presenting with a colorectal primary was 47.2 years with 35% of them aged below 40 and 80% below 60 years [6] This is in contrast to Western literature, especially in the United States, where 90% of new CRC cases are above 50 years at diagnosis and 58% of all new CRC cases are above 65 years of age [12]. Whether the increased incidence of CRC at a younger age is due to a larger proportion of young people in the population pyramid as compared to the West (which has a significant proportion of aging individuals) or whether it truly reflects an actual difference in the age at presentation is not certain. Additionally, the available Indian data originates from isolated centres in the country which may be influenced by a referral bias and not entirely indicative of the disease presentation in the general population.

3 Etiology and Risk Factors

Colorectal cancers occur in three principal forms—sporadic, familial, and hereditary. About 2–5% of colorectal cancer cases occur in the setting of defined inherited syndromes like Lynch, Familial Adenomatous polyposis, MUTYH polyposis, etc. These constitute the hereditary group. Roughly one-third of incident cases show strong familial clustering, i.e., the Familial group. These families demonstrate a number of inheritable genetic mutations with variable penetrance. Gene polymorphisms, gene modifiers, and tyrosine kinase defects are the possible inciting factors along with associated environmental influences. Acquired and genetic anomalies like the c-myc gene amplification, ras point mutations, p53 mutations, and chromosome 5, 17, 18q allelic deletions have been recognized as causative factors in carcinogenesis. Though family history accounts for the highest relative risk amongst the etiologic factors for colorectal cancer, sporadic cases are by far the largest group seen in clinical practice.

The etiopathogenesis of colorectal cancer is one of the most extensively studied entities in cancer pathology. Factors implicated in colorectal cancer pathogenesis include:

1. Distribution, nationality, race, and religion—Colorectal cancer, as mentioned, is a disease predominantly of the Western populace with factors like lifestyle, dietary habits, and rapid industrialization being implicated in its etiopathogenesis. Low-risk populations seem to have a relatively increased incidence of right-sided cancers, whereas high-risk communities have an increased risk of left-sided malignancies [13–15]. Jews have a higher incidence than any other religious community [16–19].
2. Age—The likelihood of an individual developing colon cancer increases progressively after the age of 40 with a sharp rise after 50. Incidence rates are more than 50 times higher in the seventh and eighth decades of life than in those younger than 40 years. Recent trends however show an increasing incidence among the younger population [20].
3. Dietary factors—Low-residue, high-carbohydrate diet has been shown to have a contributory role in colorectal carcinogenesis [21] Dietary fiber exerts a protective influence probably due to the abundance of inositol hexaphosphate in plant fiber which acts as a specific anti-cancer agent [22]. Another hypothesis to explain the protective influence of dietary fiber is the increase in stool bulk and dilution of putative carcinogens in the colonic lumen by more rapid transit with diminished mucosal exposure to injurious agents [23].

   High intake of animal fat and protein has been demonstrated to have a strong correlation by some investigators. Populations with high beef consumption are known to have the highest incidence of bowel cancer [24] However, this association has been controversial since other investigators have only found a weak association between CRC and the consumption of red meat or saturated fat [25].
4. Polyps—Precursor lesions found in the colon like tubular and villous adenomatous polyps are a known risk factor for developing malignancy over time. A majority of the sporadic colon cancers develop from these adenomatous polyps albeit with a long latency period of 5–10 years [26].
5. Inflammatory bowel disease—Ulcerative colitis and Crohn's disease are known risk factors for colorectal cancer. The extent of colonic involvement and the duration of colitis are directly proportional to the extent of cancer risk.
6. Fecal bile acids—High concentrations of fecal secondary bile acids like deoxycholic and lithocholic acid, typically seen in the Western diet have been confirmed by population-based studies in patients with colon cancer [27, 28]. An unambiguous relation between the fecal bile acid level and the incidence of dimethlyhydrazine-induced colon cancer has been established [29]. Hence, cholecystectomy has also been implicated as a possible precipitating factor by increasing the enterohepatic circulation of secondary bile acids [30, 31].
7. Familial colon cancer—Up to 20% of the CRC afflicted have a familial history of colorectal cancer or adenomatous polyps in one or more first-degree relatives. The risk increases with the number of relatives affected and their age at diagnosis, possibly due either to inherited genes combined with the influence of shared environmental factors [32].
8. Genetic factors—About 5 to 10% of colorectal cancers stem from recognized hereditary conditions like familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC).FAP is associated with a mutated tumor suppressor gene *APC* while HNPCC is associated with gene mutations of the DNA mismatch repair pathway i.e.*MLH1*&*MSH2* among others. Other genetic syndromes like the Peutz-Jeghers syndrome, Familial juvenile polyposis, and MUTYH-associated polyposis are also associated with increased colorectal cancer risk.

4 Clinical Presentation in India and the World

The clinical presentation of colon cancer may vary from minor but persistent changes in bowel habits to surgical emergencies like obstruction or bowel perforation. Primary symptoms, i.e., attributable to the colonic primary, include a change in bowel habits (commonest), bleeding, and abdominal pain. Distal large bowel lesions are more prone to be symptomatic than more proximal lesions. Bleeding is the second most common symptom which could be occult or overt. Chronic anemia secondary to occult intraluminal tumor bleed, often requiring blood transfusions, is a common presentation of right colon cancer. Bleeding left colon and rectal lesions tends to be overt with less alteration in the character of the blood which appears brighter. Passage of mucus either mixed with stool or blood is highly suggestive of neoplastic etiology and necessitates a complete evaluation. Abdominal pain is usually due to luminal bowel obstruction (either partial or complete), is colicky in nature, and could be associated with other symptoms like nausea, vomiting, or abdominal distension. Back pain due to retroperitoneal infiltration is a late sign. Rarely a palpable abdominal mass can be the only presenting symptom.

Systemic symptoms like significant unintentional weight loss, anorexia, fatigue, cutaneous manifestation (acanthosis nigricans, dermatomyositis, and pemphigoid), and symptoms suggestive of anemia, are all pointers towards a neoplastic colorectal etiology. A palpable left supraclavicular node (Virchow node, Toisier sign), palpably enlarged liver, jaundice (due to extensive liver parenchymal metastasis or biliary obstruction due to metastatic portal nodes), ascites, and rarely bone pain (due to bone metastasis usually in the vertebra and pelvic bones) constitute symptoms and signs of metastatic disease.

Perforation peritonitis, appendicitis due to a caecal tumor obstructing the appendiceal lumen, a perforated caecum due to an obstructing carcinoma of the distal large bowel (due to closed loop obstruction), and incarcerated hernia especially in the elderly are uncommon presentations of colonic malignancy.

5 Evaluation and Work-Up

5.1 Screening

Survival in colorectal cancer, like other gastrointestinal tumors, is a function of the stage at initial disease presentation. Colorectal cancer is largely sporadic, arising from premalignant adenomas that acquire serial genetic mutations to finally transform into the malignant phenotype, over 8–10 years [33]. This asymptomatic, pre-malignant phase provides an opportunity for screening in average-risk individuals (i.e., individuals aged 50-75 yrs. without a personal or family history of colorectal carcinoma or polyps) to detect and resect colorectal adenomas before they become malignant. A population-based screening program is only cost-effective if the disease in question is a public health problem (i.e., high incidence). The incidence of colorectal cancer in India may not at this time, warrant a nationwide population-based screening program. However, it should be noted that a large percentage of colorectal cancer cases presenting at tertiary centers are individuals <40 years old and in advanced stages of the disease [6]. Many of these individuals are treated at the village and district level for benign anorectal conditions (hemorrhoids, anal fissure, etc.) for a long period of time before being finally diagnosed as colorectal carcinoma. Perhaps adopting a 'symptom-based pathway' i.e. sigmoidoscopy/colonoscopy for symptomatic individuals (chronic lower gastrointestinal symptoms, benign anorectal disease) irrespective of age may aid in diagnosing cancer in these individuals at an earlier stage.

The majority of international guidelines, recommend screening for colorectal cancer by one of three options viz. fecal occult blood test (FOBT, mainly the fecal immunochemical test (FIT), annually or biennially), flexible sigmoidoscopy every 5 years or colonoscopy every 10 years [34].

Fecal occult blood testing (FOBT) is the only screening modality supported by evidence from prospective randomized trials. FOBT on two samples from each of three consecutive stools followed by colonoscopy if positive, has demonstrated a survival benefit (mortality reduction of 15–33%) [35]. AnnualFOBT together with a 5-yearly flexible sigmoidoscopy has been found to be superior to either modality alone. The older guaiac-based FOBT detects the presence of blood in feces through the peroxidase activity of heme. The results of this test could therefore be confounded by the presence of dietary peroxidases such as heme from the myoglobin of red meat, plant peroxidases, and even antioxidants like Vitamin C. Additionally, the test has low sensitivity for both CRC (25–38%) and advanced adenomas (16–31%) [36]. The FIT is a newer version of the guaiac FOBT with an antibody to human globin protein without any cross-reactivity to animal-derived protein. Therefore, no dietary restrictions are needed before testing. Another advantage is the specificity for colonic blood since upper GI globin is degraded by proteolytic enzymes. The FIT is, therefore, a simpler test, requiring fewer samples and with greater sensitivity for advanced adenomas and CRC than the guaiac-ased test [37].

Double-contrast barium enema (DCBE) has, for all practical purposes been relegated in today's times to the pages of history. Better investigative procedures like colonoscopy and computed tomography have virtually replaced DCBE. There are no studies to support a reduction in the incidence or mortality of CRC in average-risk individuals with DCBE [38]. The need for a subsequent colonoscopy should there be a positive finding on DCBE has made the procedure redundant. However, in the absence of expertise in colonoscopy, a 5-yearly screening with DCBE, from the age of 50 years could be employed as the next best alternative.

Flexible sigmoidoscopy has been recommended as a preferred initial tool for colorectal cancer screening [39], as the majority of colorectal cancers are in the left colon, within the reach of detection by the flexible sigmoidoscope. Additionally, complete bowel preparation is not required. A single phosphate enema is sufficient to clear the distal colon. Combining 5-yearly flexible sigmoidoscopy with annual FOBT significantly increases the yield of detection. All positive tests are followed up with a complete colonoscopy.

Colonoscopy has been universally accepted as the gold standard for colorectal cancer screening due to its sensitivity and specificity approaching 100% in experienced hands. Cancer-related mortality can be lowered by 68%–88% among individuals who undergo screening colonoscopy as compared to those who do not [40].Despite being a relatively safe procedure (risk of perforation <0.1%) that is readily available, colonoscopy does require full bowel preparation and sedation.

CT colonography (CTC) is a structural imaging test, developed in 1994where cross-sectional images of the abdomen and pelvis are obtained after insufflation of the large bowel with air or carbon dioxide. It is relatively less invasive than an optical colonoscopy, does not require anesthesia, and has an image acquisition time of about 15 seconds. Bowel preparation and rectal catheter insertion are however necessary for this technique. The CTC finds utility as a triage modality in individuals at low to medium risk for CRC subjecting patients to a complete colonoscopy only if a polypectomy is required [41].CTC could also serve as an alternative in patients who cannot undergo an optical colonoscopy due to the risk of associated complications, ongoing anticoagulation therapy, or the presence of significant co-morbidities. Overall sensitivity of over 90% for polyps >10 mm in size has been observed, although marked heterogeneity is noted among published reports [42, 43].

5.2 Work-Up

The minimum cancer staging directed work-up for a patient with suspected colon cancer would include

- Colonoscopy + biopsy.
- Imaging—Contrast-enhanced computed tomography (CECT) of the thorax, abdomen, and pelvis.
- Tumor markers—Carcinoembryonic antigen (CEA), CA19–9.

5.2.1 Colonoscopy

Optical colonoscopy is the accepted gold standard for the evaluation of colon cancer with three main advantages—complete and direct visualization of the entire colon and rectal mucosa, the ability to obtain a biopsy to establish tissue diagnosis, and the possibility of therapeutic intervention with the removal of precancerous lesions.

A complete colonoscopy is essential because there is a possibility of synchronous cancers (2–10%) or polyps (15–50%) [44–46]. With obstructing tumors, complete intubation of the colon may not be possible. In these situations, a complete colonoscopy is recommended within 6 months following definitive surgery.

High-definition, white-light, optical colonoscopy, which is the standard of care may be further enhanced with the following:

- Chromoendoscopy—An enhanced imaging technique in which contrast agents (e.g., indigo carmine) are applied locally to the mucosa during endoscopy to visualize mucosal abnormalities. The Kudo scoring system is utilized for polypoid lesions which is based on mucosal pit patterns. Improved visualization of early neoplastic lesions is a noted advantage of this technique.
- Magnification endoscopy—High-resolution magnified images for further characterization of neoplastic lesions.
- Narrow-band imaging (NBI)—The oldest established method of virtual chromoendoscopy. Conventional white light video endoscopy utilizes the entire visible spectrum while NBI is based on an integrated filter system that narrows the spectrum and accentuates the blue light spectrum thus providing a clearer contrast enhancement of the architecture of mucosal vessels.
- Intelligent color enhancement (FICE) (Fujinon) and iScan imaging (Pentax)—are processor-integrated software applications that alter the wavelength ranges of reflected light and thus offer a number of filter options to enhance mucosal lesion-detection rates.
- Autofluorescence endoscopy—Also known as the Red Flag technology, this technique is based on the concept of fluorescence produced by auto fluorophores or exogenously introduced fluorophores like 5-Aminolevulinic acid. It plays a significant role in the early detection of dysplasia.
- Endomicroscopy—The first endoscopic procedure that, in addition to the analysis of surface structure, permits microscopic analysis of cellular structures of the mucous membranes in vivo.

5.2.2 Imaging

A CECT of the thorax, abdomen, and pelvis is recommended for every patient with colon cancer. A pre-CECT confirmation of adequate renal function is mandatory before the use of intravenous (IV) contrast. Both an IV and oral contrast study is the recommended protocol. In patients in whom a CECT is contraindicated, an MRI of the abdomen and pelvis is the recommended alternative.

Colon cancer appears as enhancing mural thickening of the colonic wall. Early lesions appear as polyps (either sessile or pedunculated) while advanced cancers are usually seen as “saddle” or “apple core” lesions due to circumferential narrowing of the lumen, overhanging borders, and mucosal destruction. Every attempt should be made to determine the T, N, and M stage on baseline imaging (Table 1). The main advantage of a preoperative CECT of the thorax is that it is not only more sensitive than a conventional chest X-ray to pick up pulmonary metastasis but also provides a baseline scan for subsequent comparison should there arise a suspicion of metachronous pulmonary metastasis [47].

PET-CECT is not recommended for routine initial staging of patients with colon cancer, but may be useful in the following clinical situations:

- Evaluating the nature of indeterminate lesions detected on conventional imaging.
- A rising CEA in a patient on surveillance after completion of definitive treatment.
- In the setting of recurrent disease.

Table 1 Interpretation of a CECT for colon cancer

Establishing the T stage Enhancing mural wall thickening—likely site of primary colon cancer Pericolonic fat stranding i.e. at least T3 Frank infiltration of surrounding organs i.e.T4b—determine the feasibility of multi-visceral resection with negative margins, depending on the organs involved
Establishing the N stage Evaluate the presence of perilesional nodes, nodes along the draining vessels, and nodes along the root of the draining pedicles. Unresectable nodal disease at the root of the draining pedicle may render a patient inoperable
Establishing the M stage Evaluate for liver metastasis, nodes at the porta hepatis, non-regional (retroperitoneal) nodal metastasis, ascites, peritoneal disease, lung and bone metastasis
Look for the presence of potential surgical complications Tumour perforation (free intraperitoneal gas), intestinal obstruction (dilated bowel loops), closed-loop obstruction (left colon primary, dilated colon, collapsed small bowel)

- Detection of occult metastatic disease prior to embarking on major resections for metastatic disease.

5.2.3 Tumor Markers

Serum tumor markers(CEA and CA 19–9) are utilized in the detection, diagnosis, and treatment of patients of colon cancer.CEA finds its utility primarily as a prognostic marker after diagnosis and to monitor disease progression. Elevated CEA levels also portend a poor prognosis for resectable CRC [48]. Levels fall post tumor resection and the sensitivity is known to increase with the tumor stage [49]. The application of CEA as a screening tool is hindered by the fact that elevated levels are non-specific and can be found in benign conditions as well. Additionally, in a fraction of patients, CEA levels rise only in the advanced stages of the disease.

CA 19–9 antigen as a tumor marker is less sensitive and specific for CRC as compared to CEA. Tissue polypeptide-specific antigen (TPS) and tissue polypeptide antigen (TPA) are known to be elevated in metastatic CRC but are unsuited for screening due to low sensitivity and specificity. A combination of TPA and CEA has greater sensitivity in identifying recurrent diseases [50]. Other biomarkers of significance are circulating tumor cells, circulating DNA-based biomarkers like the cell-free DNA, its integrity and genetic alterations, microsatellite instability, detection of aberrant DNA methylation of the SEPT9 gene, RNA-based markers amongst others, with many still in the research stage.

5.3 Pathology

5.3.1 Gross Pathology

There are various patterns of growth morphology seen in colon cancer. Carcinomas of the proximal colon are for the majority, polypoid and exophytic often outgrowing their blood supply and subsequently undergoing necrosis. Tumors of the distal colon grow in a more circumferential manner with a 'napkin-ring' configuration. The fibrous stroma of the tumor is responsible for the constricting nature with resultant luminal compromise, whereas the annular or circumferential growth pattern occurs due to the circular arrangement of lymphatics along the colon wall. The clinical implication of this predilection for a circumferential growth pattern in left colon lesions is the higher incidence of obstruction in patients with distal large bowel cancer.

5.3.2 Microscopic Pathology

Adenocarcinoma originating from the epithelium of the colorectal mucosa remains the most common histology encountered. The WHO classification enlists a number of histologic variants such as mucinous, signet ring cell, medullary, micropapillary, serrated, cribriform comedo-type, adenosquamous, spindle cell, and undifferentiated. Neuroendocrine histology, lymphomas, and mesenchymal tumors are also observed, though rarely.

Invasion of the muscularis mucosae is the defining feature of invasive colorectal cancer. Although invasion through the lamina propria (basement membrane) is considered as invasive cancer at other gastrointestinal sites, in the colon and rectum, truly intramucosal lesions i.e. without breach of the muscularis mucosa (which may be involved) are considered as Tis, as the propensity for metastasis is negligible.

The degree of differentiation of conventional colorectal adenocarcinoma is defined by the degree of gland formation. Tumors with>95% gland formation are termed well differentiated, 50–95% gland formation is termed moderately differentiated, and < 50% gland forming tumors are mostly solid and are considered poorly differentiated carcinomas. Moderately differentiated adenocarcinoma is the most common histology encountered in clinical practice. Tumor grade is generally considered a stage-independent prognostic variable with high-grade tumors associated with poor survival.

Immunohistochemical markers most commonly utilized to define colorectal adenocarcinomas include cytokeratin (CK) 20, CK7, and CDX2 with positivity for CK20 and negativity for CK7 being the most prevalent immunophenotype [51] However, patterns contrary to the above are also seen. CDX2 is a marker for enteric differentiation and is positive in >90% of colorectal adenocarcinomas but lacks colorectal specificity [52].

5.4 Staging

The TNM staging system has been universally accepted as the standard staging system for colorectal cancer. Staging can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 268–269, Chapter no.20: Colon and Rectum cancer. Definition of TNM and AJCC prognostic stage groups can be accessed at https://emedicine.medscape.com/article/2006674-overview [53]. Older systems of staging e.g. Dukes, Astler-Coller, etc. are now only of historic importance. Carcinomas that arise in the colon are spread by direct invasion of the layers of the colonic wall i.e., mucosa, submucosa, muscularis propria, subserosa, and serosa. This information is employed in assigning the T stage. The N and M staging denotes the invasion of lymphatics and blood vessels ultimately resulting in metastases at regional nodes (N) and at sites distant from the primary tumor (M). The number of metastatic sites involved is an important prognostic factor for colorectal cancer. Carcinomas may also grow in the subserosal tissue as discrete nodules of cells termed tumor deposits. The eighth edition of the AJCC cancer staging manual has made the following changes from the previous versions:

- M1c—Lists peritoneal carcinomatosis as a poor prognostic factor (Level 1 evidence).
- Clarification of the definition of tumor deposits (Level II evidence).
- Lymphovascular invasion—Reintroduced the L and V elements to better identify lymphatic (L) and vessel (V) invasion.
- Clarified the importance of MSI as a prognostic and predictive factor.
- Identified KRAS, NRAS, and BRAF mutations as critical prognostic factors which are also predictive.

5.5 Referrals Including Genetic Counseling

Hereditary colorectal cancer occurs due to pathogenic germ line mutations (i.e., mutations in the germ cells (sperm/ovum) and are therefore present in every cell of the body, as against sporadic mutations which are present only in the tumor cells) which are transmitted through generations with varying degrees of penetrance. Lynch syndrome and FAP are the two most common causes of hereditary colorectal cancer. Index cases with these genetic disorders often present with colorectal cancer as the first manifestation of the syndrome. It is important to identify and accurately classify these patients as hereditary colorectal cancer vis-à-vis sporadic disease. Once the ‘syndromic’ presentation of colorectal cancer has been confirmed through the recommended algorithm of genetic testing, the rest of the family members at risk can then be evaluated for the presence of the causative gene mutation and counseled regarding the associated colorectal cancer risk. There exist well-defined screening and treatment guidelines for hereditary colorectal cancer [54] as the incidence of cancer in these families could be as high as 60–100% depending on the syndrome involved.

5.6 Lynch Syndrome

Lynch syndrome is responsible for 3% of colorectal cancer cases worldwide and occurs due to a germ line mutation in at least one of the DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2). Lynch and colleagues estimated a three-fold risk of colorectal cancer compared to the general population, in families with a first-degree relative having this condition [55].

The DNA mismatch repair system is a cellular mechanism designed to repair short segment and single base pair mismatches. The system has two counterparts, one to detect areas of base mismatch and the second to repair them. The protein products of the MMR genes do not work in isolation but dimerize in their active form and work in pairs. A deficiency of a single protein, due to a mutation in the associated gene, would render the entire system nonfunctional. The phenotypic manifestation of a defective DNA mismatch repair system is the presence of unstable microsatellites. Microsatellites are long segments of DNA comprising multiple repeats of a particular sequence of base pairs. In the presence of a defective MMR system, the lengths of these microsatellites become unequal. This is termed microsatellite instability. When inaccurate DNA replication occurs due to ineffective mismatch repair affects the genes involved in one or more cellular growth controlling pathways, it results in uncontrolled cell growth i.e. cancer.

Observed by Warthin more than a century ago, Lynch and colleagues defined two clinical variants of this syndrome [56]:

- Lynch syndrome I or HNPCC (hereditary nonpolyposis colonic cancer).
- Lynch syndrome II or HSSCC (hereditary site-specific non-polyposis colonic cancer).

Features common to both variants include an autosomal dominance pattern, multiple primary colonic tumors, early age at onset, and predominance for the proximal large bowel. Lynch syndrome II is characterized by adenocarcinomas at extracolonic sites as well, particularly the endometrium and the ovary [57]. Other extracolonic sites involved in Lynch syndrome include the pancreas, stomach, hepatobiliary system, brain (Turcot syndrome), upper urothelium, and skin i.e. sebaceous adenomas (Muir-Torre syndrome).

5.6.1 Amsterdam II Criteria

These are a set of clinical criteria to detect possible families affected with HNPCC and were formulated in 1991 [58]. They include:

- At least three relatives who have a biopsy confirmed, HNPCC-associated cancer (colorectal, endometrial, ureter, renal pelvis, small bowel).
- At least two generations are affected.
- One is the first-degree relative of the other two.
- At least one relative was diagnosed at ≤50 years of age.
- Familial adenomatous polyposis has been excluded.

The criteria have been modified to include the following:

- Two cases of colorectal cancer when families are small (one younger than 55 yrs. old).
- Two cases of colorectal cancer and one of endometrial cancer or other early-onset cancer.

5.6.2 Bethesda Guidelines

Formulated during the National Cancer Institute workshop on HNPCC in 1997 and revised in 2004, the Bethesda guidelines seek to address the underestimation of the true incidence of HNPCC by the Amsterdam criteria. They also assist in selecting patients to be analyzed for Microsatellite instability (MSI). MSI testing is recommended in individuals who meet any of the following criteria:

- Colorectal cancer is diagnosed at ≤50 years of age.
- Two HNPCC-related cancers (synchronous or metachronous).
- Colorectal cancer with MSI-H histology at ≤60 years of age.
- A first-degree relative who has HNPCC-related cancer, one of the cancers diagnosed at ≤50 years of age.
- Colorectal cancer in two or more first- or second-degree relatives with HNPCC-related tumors [59].

5.6.3 Familial Adenomatous Polyposis (FAP)

Mapped to the *APC* gene on chromosome 5q21, this hereditary polyposis syndrome is transmitted in an autosomal dominant fashion. Even though Virchow reported a 15-yr old boy with multiple colonic polyps as early as 1863, the demonstration of the *APC* gene as the responsible mutation was established only in 1986, by Lemuel Herrera. This gene has near 100% penetrance. The median age at presentation with colorectal polyps is 29 yrs. and the average age of presentation of FAP-related colorectal cancer is 39 yrs.

Characteristic features include multiple colonic polyps, gastric, duodenal a periampullary polyps with occasional extraintestinal manifestations like osteomas, brain tumors, desmoids, congenital hypertrophic retinal pigment epithelium (CHRPE) and epidermoid cysts. The presence of more than 100 adenomatous polyps in the large bowel is nearly diagnostic of FAP. Patients with multiple colonic polyps but less than 100 may have an attenuated form of the syndrome. Attenuated FAP should be suspected in a patient with a cumulative history of >10 to 20 colorectal adenomatous polyps. Gastric polyps are mostly fundic gland hyperplasia rather than adenomatous polyps and therefore have limited malignant potential. Duodenal polyps on the other hand are adenomatous and hence premalignant and confer an increased risk of periampullary carcinoma. Eponymous syndromes related to FAP are *Gardnersyndrome* (colonic polyps, epidermal inclusion cysts, and osteomas) and*Turcotsyndrome* (brain tumors like cerebellar medulloblastomas and glioblastomas).

5.6.4 Genetic Testing and Counseling

The possibility of hereditary colorectal cancer, i.e., FAP (including attenuated FAP and FAP variants) and Lynch syndrome should be suspected based on the criteria detailed above. Such individuals should then be evaluated in a dedicated genetic clinic. Detection of a pathogenic germ line mutation establishes a diagnosis of hereditary colorectal cancer and family members can then be offered genetic testing to determine whether they have inherited the same pathogenic mutation. Carriers of pathogenic mutations will benefit from increased surveillance while family members who have not inherited the mutant gene qualify as average-risk individuals and can undergo routine screening.

Failure to detect a pathogenic mutation is less helpful, as undefined, inheritable genetic processes may still be present. The *APC* gene mutation may not be identified in up to 20% of patients with a well-documented clinically evident FAP syndrome and a negative gene test result may occur in nearly 50% of families with a suspicion of Lynch syndrome. Although intensive surveillance is still recommended for such families it may however be stopped earlier if no manifestation of the disease presents itself.

6 Principles of Management

Radical surgical resection forms the mainstay in the treatment of colon cancer and is more often than not the first treatment modality to be offered. Even in the setting of locally advanced disease, surgery is recommended as the first treatment modality if an R0 resection can be achieved. This is in contrast to rectal cancer, where neoadjuvant therapy for locally advanced disease plays a vital role in reducing local recurrence. There is a dearth of evidence for neoadjuvant therapy in locally advanced colon cancer. As additional evidence from ongoing trails becomes available, the role of neoadjuvant chemotherapy in colon cancer will be further elucidated in the near future.

Probably, the most significant paradigm shift in the last decade has been the adoption of treatment with curative intent, in a select group of patients with metastatic colorectal cancer. Effective multidisciplinary treatment has offered survival rates of 45–50% in this select patient group [60–62].

The following section will present a detailed account of the role of surgery, chemotherapy, and radiation in the multidisciplinary management of colon cancer.

7 Surgical Management

7.1 Endoscopic Resection

The classical adenoma-carcinoma sequence as postulated by Vogelstein [33] states that colorectal cancer arises from adenomatous polyps which acquire sequential genetic mutations that ultimately result in the malignant phenotype, occurring over a time period of 8–10 years. This fact provides a window where in timely endoscopic resection of adenomatous polyps can preclude their malignant transformation.

Endoscopic management of colorectal polyps is achieved by two basic techniques viz. endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR is applicable for polypoid lesions and involves the injection of saline into the submucosa, creating a cushion between the mucosa and the muscularis. The elevated polyp is then resected with an electrocautery snare. The absence of a 'lift' sign on submucosal injection indicates submucosal infiltration, often precluding an endoscopic approach. ESD on the other hand utilises specialized endoscopic knives to create a mucosal incision followed by subsequent dissection in the submucosal space. This technique enables larger and more sessile lesions to be resected en-bloc. According to a recent meta-analysis, a 96.3% cure rate with endoscopic polypectomy can be achieved for polyps >2 cm, with a 1.5% perforation rate and only 8% of patients proceeding to subsequent surgery [63].

Infiltration of the muscularis mucosa into the submucosa as seen on histopathological examination of endoscopically resected polyps is required to establish a diagnosis of invasive adenocarcinoma. Purely intramucosal lesions do not show lymphatic spread and are not considered invasive. Invasive adenocarcinoma in a pedunculated polyp, resected endoscopically en-bloc with a negative margin, grade 1/2 on histology and no evidence of angiolymphatic invasion does not need any further management. These patients can be kept under surveillance. However, there is no consensus on what constitutes a negative margin on endoscopically resected polyps; 1 mm, 2 mm, or absence of malignant cells at the cauterized edge are all accepted definitions. We consider ≥1 mm a negative margin and are comfortable keeping these patients under surveillance. Should there be any one adverse factor (viz. positive margin, Grade3/4 or angiolymphatic invasion), or a piece-meal resection precluding accurate evaluation of margin status, a subsequent radical colectomy should be considered, weighing the risks and benefits of radical surgery.

Endoscopically resected sessile polyps show a higher propensity for adverse outcomes in terms of local recurrence, metastatic disease, and mortality [64–66]. However, with advanced ESD techniques, sessile polyps resected en-bloc, with negative margins and no adverse factors can be effectively managed endoscopically [67, 68]. When treating early colon cancer, another important issue to consider is the extent of submucosal infiltration. Although all submucosal infiltration is classified as T1 disease [53], the incidence of lymph node metastasis exponentially increases with the depth of submucosal involvement. Lesions involving the Upper third of the submucosa (SM1) have a 1–3% risk of lymph node metastasis. This increases to 8–10% if the middle third is involved (SM2) and may go up to 23–30% if the entire submucosa is infiltrated (SM3) [69, 70]. Therefore, endoscopic resection is only considered adequate for SM1 lesions and for that matter, an R0 endoscopic resection, even with advanced ESD is only likely in these lesions with superficial submucosal infiltration especially if they are sessile. A recent systematic review showed a very low incidence of SM1 lesions in ESD resected specimens and a still lower rate(6%) of curative resections calling for caution in the use of this technique in colorectal cancer [71].

7.2 Radical Colectomy

A radical colectomy is not a mere resection-anastomosis of the colon. Strict adherence to the basic oncological principles of an en-masse resection of the tumor along with its draining lymph nodes is mandatory to perform a radical colon resection. As the draining lymph nodes follow the vascular supply of the colon, a knowledge of the colonic blood supply is essential to be able to dissect and ligate these vessels at their origin, ensuring a radical lymphadenectomy.

The abdominal colon is supplied by the ileo-colic, right colic, middle colic, left colic and sigmoid vessels Fig. 1 The location of the primary tumor determines which vascular pedicles need to be divided which in turn defines the surgical templates for radical colonic resection (Table 2). It is also important to note what is considered regional lymph nodes for tumors at different locations in the large bowel, which can be accessed at https://training.seer.cancer.gov/colorectal/anatomy/lymph-nodes.html [53].

A standard right hemicolectomy is oncologically adequate for tumors in the caecum and ascending colon. However, if the lesion reaches the hepatic flexure the middle colic pedicle needs to be ligated at its origin, to perform an extended right hemicolectomy. Mid- transverse colon lesions can be oncologically resected with a transverse colectomy taking the middle colic vascular pedicle,

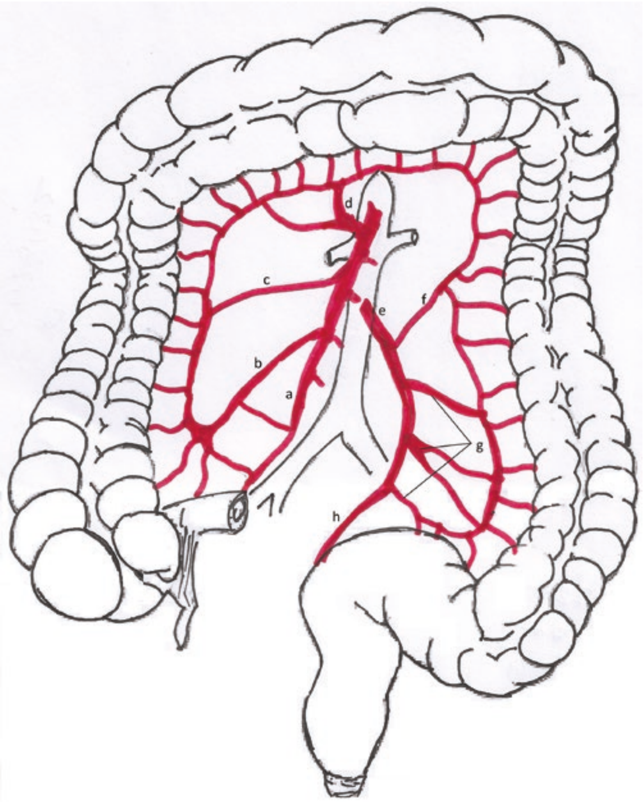


Fig. 1 Vascular anatomy of the colon

Table 2 Radical colectomy: surgical templates

Location of Primary Tumour	Vascular pedicles are to be divided	Colon resection type
Caecum and ascending colon	Ileocolic, right colic, right branch of the middle colic	Right hemicolectomy
Hepatic flexure	Ileocolic, right colic, middle colic at its origin	Right extended hemicolectomy
Transverse colon	Middle colic	Transverse colectomy
Descending colon	Left colic, left branch of the middle colic	Left hemicolectomy
Sigmoid colon	Sigmoid vessels	Sigmoid colectomy
Rectosigmoid	Sigmoid vessels, inferior mesenteric artery	Anterior resection

however, it is often technically challenging to mobilize and anastomose the hepatic and splenic flexures following resection of the transverse colon. Additionally, the colonic blood supply via the marginal artery is most tenacious at the flexures leading to a high risk of vascular compromise at the anastomosis following a transverse colectomy. Therefore, though it is oncologically adequate, a transverse colectomy is rarely performed. A right extended hemicolectomy is our preferred choice for transverse colon lesions.

Tumors between the distal transverse and proximal descending colon deserve special attention. Involvement of the distal transverse colon and/or splenic flexure theoretically necessitates resection of the main middle colic pedicle in order to remove all regional nodes. This results in a very short stump of transverse colon making the subsequent colocolic anastomosis technically difficult. An extended right hemicolectomy with ileo-descending anastomosis is oncologically adequate, and technically easier, but comes with the price of resection of additional large bowel and the ileocaecal valve with its resultant functional consequences. There is very little literature to guide the choice of procedure for tumors at this location. In a recent retrospective review from the UK, both an extended right hemicolectomy (ileocolic, right colic, middle colic and ascending branch of the left colic vessels) and left hemicolectomy (left colic and left branch of the middle colic vessels) were shown to have equivalent outcomes in terms of perioperative morbidity and overall survival, making either procedure a suitable choice for tumours at this location [72]. This was further confirmed in a systematic review and metaanalysis [73].However, in the setting of obstructing tumours at and around the splenic flexure with doubtful caecal viability, a right extended hemicolectomy would be the procedure of choice.

The inferior mesenteric nodes are considered regional nodes for tumours in the left colon (descending, sigmoid, rectosigmoid). We perform a nodal dissection right till the root of the inferior mesenteric artery (IMA) for all left colon lesions irrespective of what vascular pedicles are eventually ligated. A sigmoid colectomy, ligating the sigmoid vessels while preserving the left colic and superior rectal pedicle is oncologically adequate for lesions entirely within the sigmoid colon. While this is feasible for lesions at the apex of the sigmoid loop, we prefer to include the left colic for sigmoid tumors at or near the descending-sigmoid junction and the superior rectal artery (i.e. anterior resection) for lesions towards the rectosigmoid.

7.3 Complete Mesocolic Excision (CME)

When one considers the patterns of failure following radical colon and rectal resection it becomes evident that while both have a nearly equal propensity for liver metastasis (colon 69.6%, rectum 67.4%), Colon cancer is more likely to fail in the abdomen while rectal cancer is associated with higher incidences of lung and brain metastasis [74]. While this is largely due to the fact the colon is an entirely abdominal organ, it cannot be denied that radical resections for colon cancer have been less standardized as compared to total mesorectal excision (TME) for rectal cancer. Preservation of the mesorectal envelop is the hallmark of a complete TME, which has been shown to drastically reduce local recurrence rates [75].

Hohengerber et al. introduced a similar concept (CME) to standardize colon resection within an intact mesocolic envelop [76]. Essentially this technique has three components, namely dissection in the embryological plane to maintain an intact mesocolic envelop (Fig. 2), a central vascular tie removing all draining lymph nodes at the root of vascular pedicles(Fig. 3), and resection of a sufficient length of the adjacent large bowel (10 cm on each side) to remove all pericolic nodes.

The incidence of metastasis to lymph nodes at the root (i.e., N3 nodes as classified by the Japanese Society for Cancer of the Colon and Rectum) varies from 7–36% depending on the location of the primary tumor [77, 78]. Moreover, removal of these N3 nodes could lead to a stage migration (from Stage II to Stage III) of 4.5% with a rate of skip metastasis (i.e. involvement of more proximal lymph node stations without involvement of distal stations) of nearly 20% [79]. In view of these facts, it is logical to hypothesize that a more radical lymphadenectomy at the origin of colonic vascular pedicles would result in lower local recurrence and possibly improve survival outcomes.

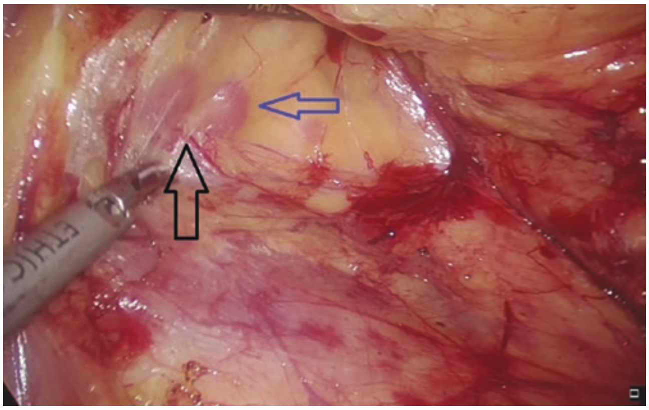


Fig. 2 Mesocolic plane in right colon CME (blue arrow—pericolic nodes; black arrow—the mesocolic plane of dissection)

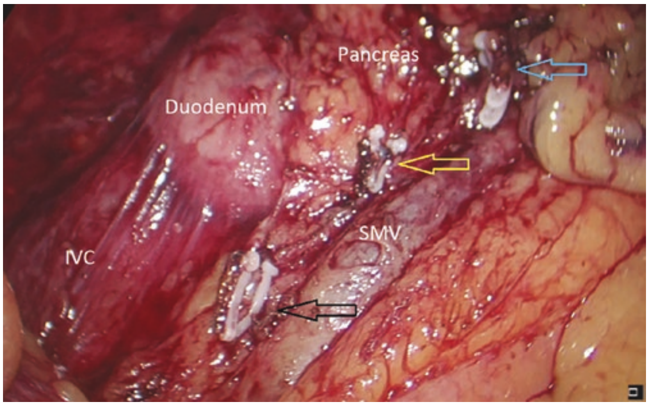


Fig. 3 Right colon bed after CME (blue arrow—middle colic pedicle; yellow arrow—right colic pedicle; black arrow—ileocolic pedicle)

There have been three systematic reviews in the last 3 years evaluating the role of CME in surgery for colon cancer [80–82]. All three reviews support a superior pathological specimen after CME as compared to conventional colectomy in terms of a longer length of resected bowel, completeness of mesocolic excision, length of the vascular pedicle, and a greater lymph node harvest. However, there is some evidence to suggest that this more radical approach could be associated with a higher incidence of injury to other organs (superior mesenteric vein, spleen, colon) [83], as well as greater intraoperative blood loss and more post-operative complications, though not translating to increased post-operative mortality [82]. Improvements in survival (disease-free survival and overall survival) and local recurrence with CME, though not uniformly reported in all series have been corroborated in a large number of reports, especially for Stage III disease [82, 84–87].

The technique also lends itself to the laparoscopic approach. A recent metaanalysis comparing laparoscopic and open complete mesocolic excision for colon cancer confirmed the equivalence of laparoscopy in terms of quality of the resected specimen, lymph node retrieval, and length of the vascular pedicle. The laparoscopic group also showed a lower rate of blood transfusions, a faster return of gastrointestinal function, fewer post-operative complications, and a better 3-year overall and disease-free survival [88]. The greater length of bowel resected and the extensive lymphadenectomy at the root of the vascular pedicles, as they take off the superior mesenteric artery and vein (with possible damage to the nerve plexus) could theoretically lead to long-term bowel dysfunction and suboptimal quality of life. However, in a population-based questionnaire study, there was no difference in the long-term bowel function and quality of life between patients undergoing CME or conventional resection for right colon cancer [89]. At the Tata Memorial Centre, we have adopted complete mesocolic excision as a standard of care for all elective radical colectomies.

7.4 The Extent of Colectomy in the Setting of Familial Colorectal Cancer

The two most common familial colorectal cancer syndromes are Familial Adenomatous Polyposis and Lynch syndrome. The surgical management of colon cancer in the setting of these syndromes differs from non-familial colon cancer in the extent of colectomy that is recommended.

For patients with colon cancer with FAP, i.e.,>100 polyps in the colon and rectum, surgical options include a total proctocolectomy (TPC) + Ileal pouch-anal anastomosis (IPAA)/ permanent ileostomy or subtotal colectomy + ileo-rectal anastomosis (IRA). In the presence of extensive colonic polyposis (i.e. >1000 polyps) TPC is recommended. However, if polyposis is not so extensive and there is evidence of rectal sparing i.e. <10 rectal adenomas all of which are amenable to endoscopic resection, a subtotal colectomy + IRA can be performed. If patients are at risk for desmoid tumor formation, TPC + IPAA is the recommended procedure as subsequent desmoid formation in the small bowel mesentery will preclude future IPAA.

Patients with colon cancer and attenuated FAP or suspected attenuated FAP i.e. >10 but <100 polyps, pose a different problem and every case needs to be managed on an individual basis. Adenomatous polyps, especially high-risk adenomas (i.e., tubular adenomas ≥10 mm, adenoma with villous histology or high-grade dysplasia) need to be resected completely. If the template of colon resection for the primary colonic tumor encompasses the polyps, these will be resected with the standard recommended colectomy as per the tumor location. If there are polyps outside the template of colonic resection they need to be removed endoscopically preferably prior to colonic resection. High-risk adenomas, not amenable to endoscopic resection may be addressed surgically at the same sitting either by extending the segment of colon resected or by full-thickness excision/segmental colectomy depending on the size and location of the polyps with respect to the primary tumor.

Patients with colon cancer with proven Lynch syndrome (documented germ line mutations in one of the DNA mismatch repair genes) or Hereditary Nonpolyposis Colorectal Cancer (HNPCC, i.e., patients or families who fulfill Amsterdam criteria for Lynch syndrome) should be offered total abdominal colectomy + IRA, irrespective of the site of colon primary [90]. As the risk of endometrial and ovarian cancer is high in women with Lynch syndrome, prophylactic hysterectomy with bilateral salpingo-oophorectomy should be offered or should at least feature in the preoperative counseling of risk vs., benefit in this group of patients.

7.5 Minimally Invasive Surgery for Colon Cancer

Minimal-invasive surgery in colorectal cancer has been in vogue since 1990 [91]. The patient benefits in terms of decreased hospital stay, decreased postoperative pain and faster recovery of bowel function are now evident. The oncological safety of laparoscopy for colon cancer, though initially a matter of concern, has now been confirmed by a number of well-conducted randomized trials. So far, there have been three main trials that have addressed the issue of laparoscopy in colon cancer namely, the COST trial [91] the COLOR trial [92], and the MRC-CLASICC trial [93].

The COST (Clinical Outcomes of Surgical Therapy Study Group) trial was a randomized, non-inferiority trial conducted over 48 institutions in North America with 872 patients [91]. The primary end point was time to tumor recurrence with overall survival (OS) and disease-free survival (DFS) as secondary end points. At the end of 3 years, the recurrence rates (RR) and OS were found to be similar—16% and 86% in the laparoscopy arm vs. 18% and 85% in the open arm respectively. There was also no difference in the time to recurrence. The recurrence rates in surgical wounds were found to be less than 1% in both the groups, laying to rest the issue of port site metastasis which was a concern at that time. The patients in the laparoscopy arm did see benefits in terms of decreased hospital stay and decreased use of parenteral (narcotics) and oral analgesics. The equivalence of laparoscopy in terms of long-term outcomes was confirmed at 5 years, with no significant difference in the DFS, OS, and RR between both the groups, finally concluding that laparoscopic colectomy for curable colon cancer is not inferior to open surgery [94].

The COLOR (COlon carcinoma Laparoscopic or Open Resection) trial was a European, multicenter, randomized, non-inferiority trial [92] conducted over 29 centers with 1076 patients. The primary end point was DFS at 3 years and the secondary end points were OS, post-operative morbidity, local recurrence (LR) at port sites, and blood loss during surgery. The pre-specified non-inferiority boundary was kept at 7% difference. They found that the 3-year DFS was 74.2% in the laparoscopy group and 76.2% in the open group and the difference in DFS was 2.0% (95% CI 3.2–7.2), the upper limit of the 95% CI for the difference just exceeding the predetermined non-inferiority boundary of 7%. However, the authors stated that as the difference in DFS between the groups was small and an as-treated analysis did not show a significant difference in DFS. the implementation of laparoscopic surgery into daily practice was justified. Additionally, the 3-year OS was also not significantly different between the groups—81.8% (lap) vs. 84.2% (open) [95]. A 10-year unplanned follow-up study with only 256 Dutch patients was reported in 2017 which concluded that laparoscopic surgery for non-metastatic colon cancer is associated with similar rates of DFS, OS, and recurrences as open surgery at 10-year long-term follow-up [96].

The third important trial was the MRC-CLASICC trial (Medical Research Council trial of Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer) [93] conducted in the UK over 27 centers with 794 patients for both colon and rectal cancers. The primary short-term endpoints were mainly circumferential radial margin (CRM) positivity, longitudinal margin positivity, and in-hospital mortality rates. The secondary short-term endpoints were complication rates, quality of life (QOL), and intra-op transfusion requirements. The primary long-term end points were 3-year OS, 3-year DFS, and 3-year local recurrence rates. There was no difference in the in-hospital mortality rates overall and the rates of positive resection margins were also similar. The CRM rate for colon cancer was 5% vs. 7% (open vs. lap) which was not significant. Complication rates or transfusion requirements also did not differ between the groups. On 3 years [97], 5 years [98], and 10 years [99] follow-up, there was no difference in OS, DFS, and recurrence rates between both the groups. At the 10-year follow-up, intra operative conversions were associated with worse OS and DFS, and right colonic cancers showed an increased propensity for local recurrence vis-a-vis left colonic lesions (14.7 vs. 5.2% ($P = 0.019$) [99].

With all three trials reporting similar short- and long-term outcomes, laparoscopy for colon cancer can be considered equivalent to open surgery at centers that demonstrate the required expertise.

7.6 Management of the Obstructed Colon Primary

About 15–40% of patients with colon cancer present as a surgical emergency with perforation or obstruction. Left-sided colonic lesions are more prone to cause obstruction vis-a-vis right colon lesions due to the smaller luminal diameter of the left colon and the more solid consistency of the stool at this portion of the bowel. Rarely, a right colon lesion can also lead to obstruction especially if it is in close proximity to the ileocaecal valve. Obstructing right colon lesions can usually be managed with a radical right colon resection and primary anastomosis in the majority of cases.

The management of an obstructing left colon primary poses a unique challenge as both the emergent nature of the surgical obstruction and the management of the malignancy need to be addressed. Additionally, there is rarely time to subject these patients to a complete staging protocol. Every patient with an obstructing colon primary is unique, with varying degrees and durations of obstruction, differing hemodynamic responses, varied co-morbid illnesses, and different levels of surgical fitness. Therefore, a uniform algorithm cannot be recommended for all such patients, rather, there exist a number of surgical options as discussed below, that can be considered in the management of these patients.

7.6.1 Diversion Colostomy

A diversion colostomy is aimed only at tiding over the surgical obstruction and is associated with the least surgical stress among all available surgical options. Although this may be the best option in the elderly, frail, malnourished, or hemodynamically unstable patient, for the large majority, resection of the primary obstructing lesion can be achieved without an increase in morbidity or mortality [100]. Care must be taken to confirm the viability of the large bowel on the exploration of every patent with an obstructing colon primary. A closed-loop obstruction (due to a competent ileocaecal valve) of substantial duration with colonic dilatation near 10 cm may lead to colonic wall ischemia and impending perforations. Colonic resection remains the only viable surgical option in the presence of non-viable bowel.

7.6.2 Hartmann's Procedure

A Hartmann procedure achieves a radical resection of the colonic primary at the same time avoiding the risk of an anastomotic leak. This approach is preferred whenever there exists a high possibility of an anastomotic leak, long-standing obstruction with an oedematous bowel wall precluding a primary anastomosis, an unfit or malnourished patient, or in the presence of hemodynamic instability.

A Hartmann procedure requires a second operation to re-establish intestinal continuity. These patients may face stoma complications like prolapse and stenosis and nearly one-third of patients with Hartmann's procedure may never have their stoma reversed [101]. Hartmann reversal is a technically demanding procedure, especially in cases of a short residual rectal stump, and is associated with leak rates of nearly 16% [102]. It is for these reasons that primary anastomosis is preferred whenever feasible.

7.6.3 Primary Resection and Anastomosis

In uncomplicated left-sided malignant bowel obstruction, a primary resection and anastomosis have been shown to be safe and feasible and are the preferred surgical approaches [103]. However, it is universally accepted that some form of colonic decompression, either manual decompression or on-table colonic lavage is mandatory prior to a colo-colic anastomosis in a one-stage procedure for obstructed left colon cancers [104]. Both manual decompression and on-table colonic lavage are equally effective in achieving colonic decompression in this setting [105–107]. A third option is to perform a subtotal colectomy with a ileo-colic anastomosis. This would effectively remove the obstructed and fecal-loaded colon and achieve as it were a "surgical decompression." Although one randomized trial [108] showed no difference in morbidity and mortality between on-table colonic lavage and subtotal colectomy, subtotal colectomy was associated with a greater number of bowel motions post-operatively. We prefer on-table colonic lavage or manual decompression with primary anastomosis for uncomplicated malignant left colon obstruction and reserve subtotal colectomy in situations of questionable viability of the proximal large bowel, synchronous lesions, and in the setting of known hereditary cancer syndromes.

7.6.4 Endoscopic Colonic Stenting

Deployment of self-expanding metallic stents across the obstructing colonic lesion serves as an effective way to tide over the surgical emergency, appropriately stage the disease, and offer the patient a one-stage definitive surgical resection in the majority of cases. Although this technique does require expertise, 85% of patients can be successfully decompressed using endoscopic stents as a bridge to surgery and 95% of these patients will have a one-sage colon resection in the following 9–10 days [109]. The use of endoscopic stents as a bridge to surgery is associated with lower post-op complications, a lower stoma rate, and a lower incidence of surgical site infection [110]. Additionally, a subsequent laparoscopic colon resection is also feasible [111].

7.6.5 Multivisceral Resection for Colon Cancer

Nearly 10% of patients with colon cancer will present with locally advanced disease invading adjacent organs [112]. More often than not this will be appreciated intraoperatively as adherence to adjacent organs. A contemporary series of multi-visceral resections for colon cancer reported a 63.6% incidence of actual tumor involvement on final histopathology [113]. Given the high percentage of pathological T4b on final histopathology, and the inferior outcomes associated with the dissection of such adhesions [114, 115], as a surgical principle, it is prudent not to disengage such tumor adherence but rather consider a multi-visceral resection where ever feasible.

For locally advanced primary colon cancer, the most common organs to be involved are the abdominal wall and small bowel [114, 116, 117] which can be resected without additional morbidity. However, the sigmoid colon, duodenum, pancreas, spleen, stomach, and bladder can all be involved depending on the location of the primary tumor. The feasibility of a multi-visceral resection has been shown in a number of reports [113, 116–119]. However, these are complex procedures associated with higher morbidity rates of nearly 25% to 49% and a post-operative mortality of nearly 7% [116, 118, 120]. A careful evaluation of the risks and benefits on a case-to-case basis is warranted when considering such an approach. Although associated with higher morbidity, if an Ro resection can be accomplished, 5-year survival rates of 80–86% [113, 116] can be achieved. When compared with a standard colectomy stage for stage, similar 5-year survival rates are observed [114, 118, 121].

Perhaps the most challenging of all multi-visceral resections for locally advanced colon cancer is an en-bloc pancreaticoduodenectomy for right colon lesions infiltrating the duodenum or pancreatic head. In many instances, the lateral wall of the duodenum may be resected en-masse with the primary at the point of infiltration, achieving an R0 resection and at the same time avoiding the morbidity of an en-bloc pancreaticoduodenectomy. Duodenal closure may be achieved either primarily or with the help of a roux-en-y jejunal loop, depending on the magnitude of the duodenal defect. Although there is a report that suggests that such lesser resections could be associated with an inferior outcome viv-s-vis a formal pancreaticoduodenectomy [122], data on this rare clinical situation is sparse and a multidisciplinary decision needs to be made on a case-to-case basis. However, though associated with more morbidity, an en-block pancreaticoduodenectomy is not associated with increased postoperative mortality and perhaps offers the best outcomes at centers with the required expertise [122–124].

7.6.6 Surgical Management of Metastatic Colon Cancer

Nearly 50% of patients with colorectal cancer will develop metastatic disease at some point during their lifetime. Metastatic disease at initial presentation may occur in 20% of patients. These patients have a worse prognosis as compared to patients with a metachronous presentation [125]. Modern polyagent chemotherapy alone can offer a median survival of 30 months [126]. This may be further enhanced with the addition of targeted agents. Surgical resection of metastatic disease offers a survival advantage in a select group of patients. As there are numerous treatment options available and variations in the sequence in which they are administered, patients with metastatic disease are best evaluated in a multidisciplinary clinic. The liver (69.6%), lung (30,7%), and peritoneum (28.8%) are the three most common sites of metastasis in colon cancer [74]. A detailed description of the surgical management of metastatic disease at these three subsites is beyond the scope of this chapter, however, only the essential principles will be presented here.

Perhaps the first issue to be resolved in the evaluation of a patient with stage IV colon cancer is the determination of treatment intent, i.e., palliative or curative. Treatment with curative intent can be offered to patients in whom the primary along with all sites of metastatic disease are resectable or amenable to some modality of definitive local treatment. A metastatic disease that is evidently unresectable at the outset would, as a general rule, be treated with chemotherapy with palliative intent. There are a small group of patients who though unresectable at presentation, may become resectable after a good response to systemic chemotherapy. At the outset these, patients are best labeled “potentially resectable” and their final treatment intent is decided on the response to systemic chemotherapy.

The second issue to consider is whether the colon primary is symptomatic or not. Intraluminal bleeding (often requiring multiple blood transfusions) and luminal obstruction are the two most common presentations of a symptomatic primary. Bleeding and obstructing lesions can be effectively managed by resection. However, in the setting of unresectable metastatic disease or a bulky primary with frank T4b disease on radiological imaging, a proximal diversion stoma would be the more prudent option. Asymptomatic primaries in the setting of the unresectable metastatic disease usually do not require surgical intervention, as >90% of these tumors never become symptomatic during chemotherapy [127]. Resection of the primary may be considered if using bevacizumab due to the risk of tumor perforation [128, 129]. It cannot be overemphasized that the treatment plan has to be individualized for every patient with stage IV colon cancer and this is best done in a multidisciplinary clinic.

7.6.7 Surgical Options for Liver Metastases

Only about 10–30% of liver metastases are resectable at presentation [130, 131]. However, 70–80% of patients will show some clinical response to systemic chemotherapy [132]. Coupled with local ablative therapies, a small number of initially unresectable liver metastasis may ultimately be feasible for metastasectomy [133]. The 5-year survival with chemotherapy and liver resection is roughly 50% [134]. Unfortunately, nearly 80% of patients undergoing liver metastasectomy will have intrahepatic recurrence at some point [135].

Options for liver-directed therapy include surgical resection and local ablative therapy with radiofrequency or microwave ablation. Surgical resection is preferred over local ablative therapies as it is associated with better long-term outcomes. Radiofrequency/microwave ablation could be considered for lesions <3 cm especially in deep-seated, centrally located lesions, patients unfit for liver metastasectomy, in conjunction with hepatectomy in patients with bilobar disease, and in the setting of unresectable disease along with systemic chemotherapy.

Liver resection may be in the form of a major hepatectomy (four or more segments [136]), less than a major hepatectomy, or extended hepatic resection. The two main issues to be considered when planning a liver resection for colorectal liver metastasis are the need for a margin negative resection and the preservation of adequate liver volume and function. In a normal liver, at least 20% of the total liver volume is required in the liver remnant following resection. This is increased to at least 30% in the presence of chemotherapy-associated liver injury and 40% in the presence of hepatic fibrosis/cirrhosis. Care should be taken to ensure at least two contiguous liver segments with intact portal and arterial inflow, venous outflow, and biliary drainage. Liver metastasectomy is generally contraindicated in the presence of unresectable extrahepatic metastasis, significant portal lymphadenopathy, progressive disease if pre-operative chemotherapy is used, and in the patient unfit for major surgery.

Liver lesions <2 cm may not be visible on imaging or intraoperative ultrasound in 10–38% of cases [137]. However, these are rarely complete responses and residual viable malignant cells can be demonstrated in 80% of these 'vanishing' lesions [138]. One option is to coil localize these small liver lesions prior to the administration of chemotherapy. This is an outpatient procedure where a small metallic coil is introduced into or adjacent to the lesion usually under ultrasound guidance. This serves as a marker for future liver-directed therapy should the lesion disappear after chemotherapy.

Synchronous liver metastasis poses a unique problem with respect to the timing of liver metastasectomy with respect to the resection of the primary. There exist three options; the conventional approach (colon resection, followed by liver resection with or without chemotherapy in the interim); the synchronous resection (both colon and liver at the same sitting),and the liver first approach (liver resection followed by colectomy with or without chemotherapy in the interim). A synchronous approach when resection of up to three liver segments is involved is generally considered safe and feasible [139, 140]. However, a combination of a major hepatic lobectomy with complex colorectal resection may lead to increased morbidity [139, 141, 142]. The liver first approach is particularly suitable for a small primary with large volume but resectable liver disease. The main concern here is the fact that chemotherapy-associated liver injury after numerous cycles may preclude subsequent major liver resection. The liver-first approach has shown to be both safe and feasible and has been adopted at some centers as a standard of care [143–145]. A number of meta-analyses supported a synchronous approach for resection of colorectal liver metastasis [146] even in patients undergoing major hepatectomy with complex colorectal resection [147, 148]. However, it should be noted that this is data from high-volume centers where multidisciplinary teams are involved in the management of these patients. To summarize, wherever feasible a synchronous approach is preferred. If not feasible a staged approach with either colon or liver first is acceptable.

7.7 Surgical Options for Lung Metastases

Lung metastasis in colorectal cancer is rarely seen in isolation and usually present in conjunction with other metastatic sites [149]. Rectal cancer has a higher propensity for pulmonary metastasis as compared to a colon primary [74]. The 5-year survival rates after pulmonary metastasectomy range from 24–56% [150]. However, recurrences are common and can be as high as 80% at 2 years [151].

Pulmonary wedge resection with negative margins can be achieved in the majority of patients with very few requiring formal lobectomy to achieve negative margins. Local ablative techniques with radiofrequency and microwave ablation are also applicable in the lung in select cases and can be utilized if repeat metastasectomy is not feasible or if competing c0-mormid illnesses preclude surgical resection.

7.8 Surgical Options for Colorectal Peritoneal Metastasis

The incidence of peritoneal metastasis in colorectal cancer is about 8–20% [152]. Peritoneal metastasis has the worst prognosis among other metastatic sites with very few patients actually achieving long-term control [153]. In the past, peritoneal metastasis from colorectal cancer was treated with palliative intent. Today a subgroup of patients can be offered cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC)with results that supersede those of systemic chemotherapy alone.

Cytoreductive surgery was popularised by Sugarbaker [154] and forms the mainstay in this treatment modality. Essentially this technique involves a detailed exploration of the entire peritoneal cavity to accurately establish the volume of peritoneal disease which is objectively scored with the Peritoneal Carcinomatosis Index (PCI) (Fig. 4) [155]. An attempt is then made to resect all macroscopic peritoneal disease which may involve stripping of all visceral peritoneum and multiple organ resections as per a defined procedure [156]. The residual disease and the end of this part of the procedure are scored on a completeness of cytoreduction score (CC Score, Table 3) [155, 157]. The best results are seen if CC-o or CC-1 can be achieved. A cut-off of 2.5 mm as the maximum residual tumor size after CRS has probably been determined by the maximum depth of drug penetration during HIPEC [158]. There is no consensus on the drug, dose, temperature, or contact time for HIPEC with each center adopting its own protocol. Oxaliplatin, carboplatin, doxorubicin, and irinotecan, using a perfusate volume of 2–5 L, at a temperature of 40–43 degrees centigrade for a contact time of 30–120 min have been used. Following HIPEC the residual solution is evacuated, the peritoneal cavity irrigated and the abdomen closed to complete the procedure.

Patient selection both from a disease volume standpoint, i.e., PCI and with respect to surgical fitness are essential for a favorable outcome and these cases are best discussed in a multidisciplinary clinic. A PCI >15–17 is generally a contraindication for CRS + HIPEC as these patients are associated with the worst prognosis. A consensus statement [159] from leading centers in CRS + HIPEC stated 8 factors that increased the probability of achieving complete cytoreduction viz. ECOG status ≤2, no evidence of extra-abdominal metastasis, up to 3 small, resectable, liver metastasis, no evidence of biliary obstruction, no evidence of ureteral

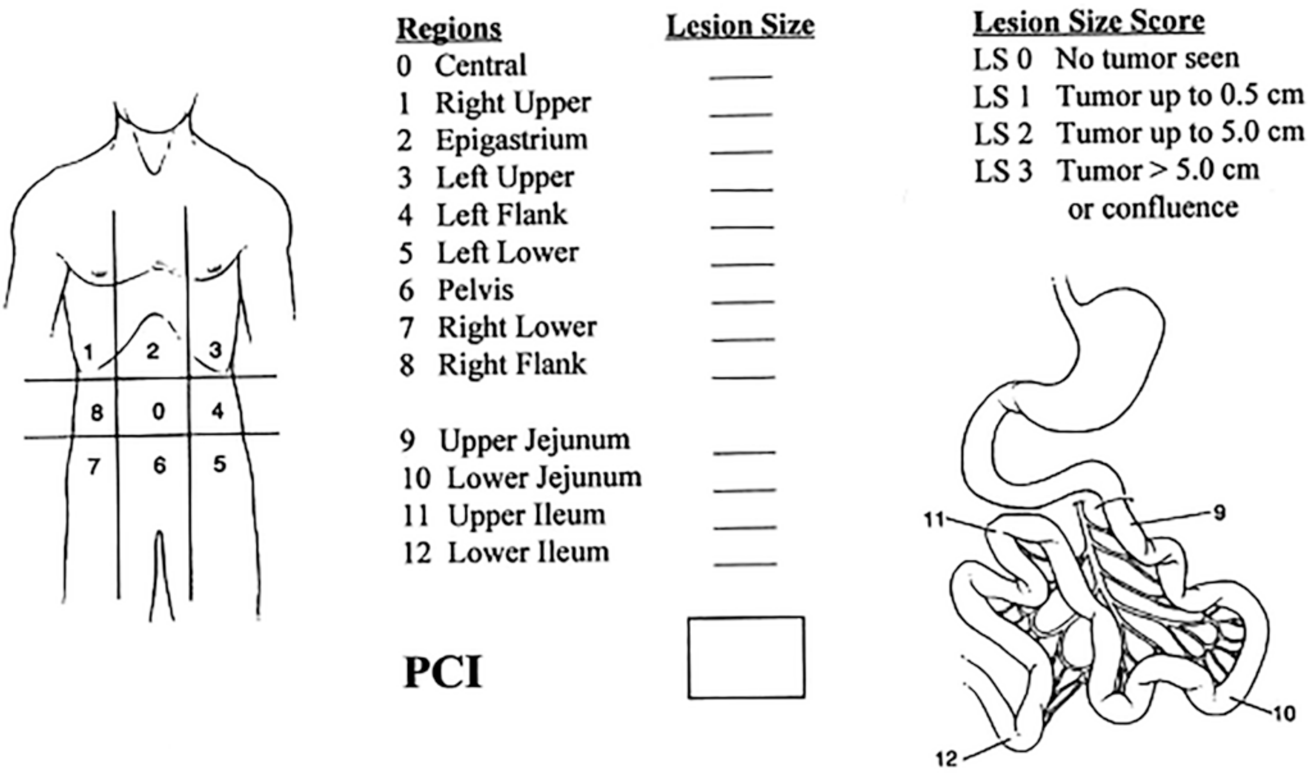

Regions
0 Central
1 Right Upper
2 Epigastrium
3 Left Upper
4 Left Flank
5 Left Lower
6 Pelvis
7 Right Lower
8 Right Flank
9 Upper Jejunum
10 Lower Jejunum
11 Upper Ileum
12 Lower Ileum
PCI
Lesion Size
Lesion Size Score
LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence
1
2
3
8
0
4
7
6
5
11
9
10
12

Fig. 4 Peritoneal carcinomatosis index

Table 3 Completeness of cytoreduction score

Sugarbaker's completeness of cytoreduction score		
Score	Definition	
CC—0	No visible peritoneal carcinomatosis after cytoreductive surgery (CRS)	CC—0 No disease
CC—1	Nodules persisting <2.5 mm after CRS	CC—1 Present 0.25 mm
CC—2	Nodules persisting between 2.5 mm and 2.5 cm	CC—2 0.25 mm 2.5 cm
CC—3	Nodules persisting >2.5 cm	CC—3 > 2.5 cm

Table 4 Contemporary series of CRS + HIPEC in colorectal peritoneal carcinomatosis

Author, year	No. of patients	HIPEC technique	Median OS (months)	5-year OS	Morbidity (%)	Mortality (%)
Glehen et al. (2004) (patients with complete CRS)	506 (28 institutions)	HIPEC + EPIC, various schedules	32.4	31	22.9	4
Verwaal et al. 2008 (RCT)	105	Open, MMC	48	45	19	8
Elias et al. (2009) (patients with complete CRS)	48 (single Centre)	Oxaliplatin 460 mg/m^2, 43°, 30 min, bidirectional	62.7	51	NR	NR
Elias et al. (2010)	523 (23 institutions)	HIPEC + EPIC, various agents	30.1	27	31	3.3
Kuijpers et al. (2013)	660	Open, MMC/oxaliplatin	33	31	34	3

HIPEC hyperthermic intraperitoneal chemotherapy, *EPIC* early postoperative intraperitoneal chemotherapy, *MMC* mitomycin

obstruction, no evidence of intestinal obstruction at >1 site, limited small bowel involvement and small volume disease in the gastrohepatic ligament.

The only randomized controlled trial reported to date is by Verwaal et al. [160]. In this study 105 patients were randomized into 2 arms—Systemic chemotherapy (5FU + Leucovorin)with or without palliative surgery or the experimental arm of CRS + HIPEC followed by the same systemic chemotherapy. The primary endpoint was survival. At a median follow-up of 21.6 months, the median survival was 12.6 months in the standard arm and 22.3 months in the experimental arm ($p = 0.32$). CRS + HIPEC was associated with a treatment-related mortality of 8%. Intestinal leakage and fistula were the main morbidity. The best results were seen in patients with involvement of up to 5 regions of the abdomen and in patients in whom all macroscopic diseases could be surgically excised. The group published their results after an 8-year follow-up [161] which showed that there were 4 patients still alive in the standard arm (2 with and 2 without disease), and 5 patients alive in the HIPEC arm (2 with and 3 without disease). However, the median progression-free survival was 7.7 months in the standard arm and 12.6 months in the HIPEC arm ($p = 0.02$). A 5-year survival of 45% was observed in patients in whom an R1 resection was possible. The authors concluded that CRS + HIPEC significantly adds survival time to patients with colorectal peritoneal carcinomatosis. The results of other contemporary series are presented in Table 4 [161–165].

It should be appreciated that CRS + HIPEC is a major surgical undertaking requiring the expertise of a specialized team. Even in the best of centers the procedure is associated with morbidity rates of 30–40%, readmission rates of 11%, reoperation rates of 10%, and a mortality rate of 2% [166]. However, with many studies presenting a median survival of 30–40 months, CRS + HIPEC should be offered to a select group of patients with colorectal peritoneal carcinomatosis, at centers with the desired expertise after in-depth counseling regarding the nature of the procedure, the associated morbidity, and the expected results.

8 Medical Management

Surgery is the first line of management for resectable colon cancer. The role of chemotherapy is largely restricted to the adjuvant and metastatic setting. Neo-adjuvant chemotherapy (NACT) for locally advanced T4b colonic primaries with frank adjacent organ infiltration has not been adequately explored. Only two studies have been reported until now for NACT in locally advanced colon cancer i.e. a pilot study [167] and a phase II study [168]. Both these studies have confirmed the feasibility, acceptable toxicity, and perioperative morbidity and have shown initial results of tumor downstaging, fewer incomplete resections, reduced apical lymph node metastasis [167], and a possible benefit of avoiding adjuvant chemotherapy, in patients with good response [168]. However, until further evidence is available, the role of chemotherapy in colon cancer is largely restricted to the adjuvant and metastatic settings.

8.1 Role of Adjuvant Chemotherapy in Colon Cancer

The goal of adjuvant therapy is to address potential microscopic metastatic cancer cells after curative surgery, thereby decreasing local and distant recurrence and increasing overall survival (OS). Adjuvant therapy in colon cancer was first introduced into clinical practice in the early 1960s, soon after the anti-cancer efficacy of 5-FU was demonstrated.

Two main treatment regimens of bolus 5-FU plus leucovorin were in vogue in the mid-1990s; the Mayo regimen (daily bolus FU/leucovorin for 5 days every 4–5 weeks) and the Roswell Park regimen (weekly bolus FU/leucovorin for 4 weeks in a 6-week cycle); both were administered for 6 months. The Multicenter International Study of Oxaliplatin/5-FU/leucovorin in the Adjuvant Treatment of Colon Cancer trial (MOSAIC) has shown that in terms of 3-year DFS, oxaliplatin plus infusional 5-FU and LV (FOLFOX) is superior to 5-FU with LV [169].

The DFS benefit for FOLFOX compared with 5-FU and LV alone was approximately 3.5%.

in unselected patients, with stage II disease. However, it exceeded 5%, for patients with stage II tumors with high-risk features like undifferentiated tumors, T4, perforation, obstruction, fewer than 12 lymph nodes identified, and presence of angio-lymphatic invasion. An update of the MOSAIC trial has shown a significant improvement in 6-year OS for patients with stage III colon cancer. However, such benefit was not seen for patients with stage II colon cancer when an oxaliplatin-based regimen was used as adjuvant therapy [170].

The XELOXA trial (oxaliplatin/capecitabine [XELOX] vs. bolus 5-FU/LV), showed the role of oxaliplatin as an important component of adjuvant therapy in stage III colon cancer with significant improvements in DFS (HR, 0.80; 95% CI; 0.69–0.93; $p = 0.0045$) and a trend towards improved OS at 5 years [171]. Based on the results of the XELOXA trial, the standard adjuvant chemotherapy for stage III colon cancer is an oxaliplatin-based regimen (FOLFOX, XELOX, or bolus 5-FU/folinic acid/oxaliplatin [FLOX]) administered for 6 months.

To alleviate the long-term neurotoxic side effects of oxaliplatin-based adjuvant therapy, the International Duration Evaluation of Adjuvant chemotherapy (IDEA) collaboration was established to prospectively combine and analyze the data from six randomized trials conducted around the world to find the answer to the question that a 3-month course of oxaliplatin-based adjuvant therapy is non-inferior to the current standard 6-month treatment for patients with stage III colon cancer. Subgroup analyses suggested that 3 months of adjuvant therapy may be non-inferior for low-risk stage III colon cancer (e.g., pT1–3 N1); whereas for high-risk stage III diseases (T4 or N2+), 6 months of adjuvant oxaliplatin-based therapy is the standard of care [172].

The role of adjuvant chemotherapy remains controversial for patients with Stage II colon cancer. A trend towards improved recurrence-free survival and OS was demonstrated in the results of a series of clinical trials. Retrospective analyses of large adjuvant trials and pooled data sets have shown remarkably consistent results that patients with stage II disease and MSI-high tumors, which represent tumors of the deficient mismatch repair phenotype (d-MMR), have an excellent prognosis and do not require adjuvant chemotherapy [173–175]. The development of a molecular profile of prognostic variables that could potentially guide adjuvant treatment decisions in stage II colon cancer is underway [174]. Gene expression signatures such as the Oncotype DX Colon and ColoPrint are included in these tests [176].

The role of novel targeted agents, such as Bevacizumab (an anti-VEGF) and Cetuximab (an anti-EGFR) has been investigated in the adjuvant setting in ongoing large phase II trials of advanced colorectal cancers. Bevacizumab and Cetuximab are not recommended in the adjuvant therapy of colon cancer outside of clinical trials, as of now. For early-stage colon cancer, randomized trials are on the way to evaluate the role of aspirin and celecoxib as adjunctive therapy with standard surgery and adjuvant chemotherapy.

In summary, for stage III colon cancer, adjuvant chemotherapy with an oxaliplatin-based regimen is the standard of care. Due to the marginal benefit in some subgroups, the role of adjuvant therapy in stage II colon cancer should involve shared decision-making. After completion of adjuvant therapy, important aspects like lifestyle changes, diet, exercise, and the use of anti-inflammatory agents must be discussed with the patients.

8.2 Role of Chemotherapy in Metastatic Colorectal Cancer

The prognosis for stage IV disease without therapy is usually poor with a median survival of 5–6 months. The addition of Oxaliplatin/Irinotecan to 5-FU/LV resulted in an improvement in median survival to around 24 months. Until 2000, the standard first-line therapy for metastatic colon cancer was 5-FU/LV as a bio-modulator and activator. Later on, Oxaliplatin/Irinotecan along with 5FU + LV have been investigated in many trials.FOLFOX, CAPEOX, and FOLFIRI regimens are FDA approved standard-of-care regimens, for first-line treatment in the metastatic setting.

The introduction of biological agents, such as bevacizumab, cetuximab, and panitumumab, has enhanced the efficacy of systemic therapy. These biological agents block one of two receptor sites viz. the VEGF (vascular endothelial growth factor) or the EGFR (epidermal growth factor receptor). Bevacizumab, Ramucirumab and Ziv-aflibercept block VEGF. The addition of Bevacizumab has shown clinical efficacy in several trials for the treatment of metastatic colorectal cancer in terms of response rates, PFS and OS in the first-line setting. Ramucirumab is a human monoclonal antibody directed against the VEGF receptor-2. Along with FOLFIRI it has been evaluated as a second-line therapy for patients, pre-treated with a fluoropyrimidine plus oxaliplatin and bevacizumab, and has shown improved OS (median OS, 13.3 months vs. 11.7 months; HR, 0.8; 95% CI; 0.73, 0.98; $p = 0.022$) and PFS [177]. Ziv-aflibercept (VEGF-Trap) was tested as a second-line treatment in a trial among patients who had all failed oxaliplatin-based first-line chemotherapy with favorable results [178].

Anti-EGFR antibodies, Cetuximab and Panitumumab have been tested as components of first-line therapy in combination with chemotherapy regimens, such as FOLFOX and FOLFIRI. It is now evident that patients with metastatic colorectal cancer must have a tumor that is wild type (i.e., non-mutated) for both K-RAS and N-RAS for these EGFR antibodies to be effective [179, 180]. There are no data to support a switch from one EGFR antibody to the other in the case of tumor progression, however, panitumumab can be considered for patients with allergic reactions to cetuximab. Currently, no difference is evident in outcome between first-line chemotherapy with bevacizumab or cetuximab. So, the treatment approach can be adjusted depending on patient and physician preference, the aim of therapy, the side-effect profile, and the cost of the therapy.

BRAF V600E (i.e., Valine(V) substituted for glutamate(E) at codon 600) mutations are found in about 5% to 10% of patients with colorectal cancer. BRAF mutations are usually, mutually exclusive with RAS mutations and are consistently associated with poor prognosis [181, 182]. The median survival of patients with BRAF-mutated stage IV colorectal cancer is 12–14 months [181]. Recent data suggests that an aggressive first-line treatment approach, with a triplet chemotherapy combination (FOLFOXIRI) plus bevacizumab might counteract the poor prognosis of this tumor genotype, to some extent [183, 184].

Regorafenib, a tyrosine kinase inhibitor that blocks the VEGF receptor, has been approved as salvage therapy in patients with metastatic colorectal cancer who have previously been treated with a 5-FU, oxaliplatin, irinotecan, and Cetuximab/Panitumumab [185].

Immune checkpoint inhibitors targeting the PD-1 pathway by binding to PD-1 or its ligand (PD-L1/L2) have shown efficacy in metastatic colorectal cancer. MSI-H/dMMR colon cancers are commonly characterized by dense lymphocytic infiltrates, which indicates a potential activation of the host's immune system [186, 187]. Based on these observations, a pilot study was initiated to investigate the role of Pembrolizumab, an antibody against PD-1, in heavily pre-treated patients with advanced colorectal cancer, classified by their MSI status. Monotherapy with Pembrolizumab showed remarkable activity, only in patients with MSI-H/dMMR cancers independent of their histology. So it is approved for MSI-H/dMMR tumors following prior treatment with a 5-FU, oxaliplatin, and irinotecan [188]. A subgroup of BRAF mutant colorectal cancer is dMMR and, therefore, a candidate for immunotherapy.

NACT can be used to downsize unresectable metastases to make them amenable to surgery. It has been shown that the OS of patients, who undergo successful NACT with subsequent R0 resection of liver metastases, is almost similar to the survival of patients with initially resectable metastases [189, 190].

To summarize, patients with stage IV disease have a chance of cure if an R0 resection is feasible at all metastatic sites. Various cytotoxic drugs (fluoropyrimidines, oxaliplatin, and irinotecan) and targeted agents (bevacizumab, aflibercept, regorafenib, as well as cetuximab and panitumumab in RAS wild-type cancers) have shown proof of efficacy for metastatic colorectal cancer. Expanded RAS mutation testing for mutations in KRAS and NRAS is mandatory before the use of EGFR monoclonal antibodies. There is no single standard of care first-line regimen for the management of metastatic colon cancer. Group decision-making is required which involves molecular and histologic assessment of the tumor, aim of the treatment, anticipated toxicity, and cost of therapy.

9 Radiation Management

The role of radiotherapy in colon cancer is very limited. Adjuvant radiotherapy is only recommended for tumors with positive or close retroperitoneal margins. This is only relevant in the caecum/ascending or descending colon, in tumors with posterior infiltration into the retroperitoneal structures where an R0 resection has not been achieved.

Palliative radiotherapy has a role in symptomatic bony metastasis, and unresectable, bleeding tumors.

10 Stage-Wise Management Algorithm

Stage I (T1/T2, N0, M0)—Radical colectomy → surveillance.

Stage II (T3/T4, N0, M0)—Radical colectomy → may consider adjuvant chemotherapy in high-risk stage II (i.e., poorly differentiated tumour (without MSI—H), obstruction, perforation, lymph node yield<12, lymphovascular invasion, perineural invasion) → surveillance.

Stage III (T1–4, N1–2, M0)—Radical colectomy → 6 months of adjuvant chemotherapy (5FU + Oxaliplatin) → surveillance.

Stage IV (Any T, Any N, M1)—Multidisciplinary management (refer to Sect. 12).

11 Stage-Wise Prognosis with Current Treatment

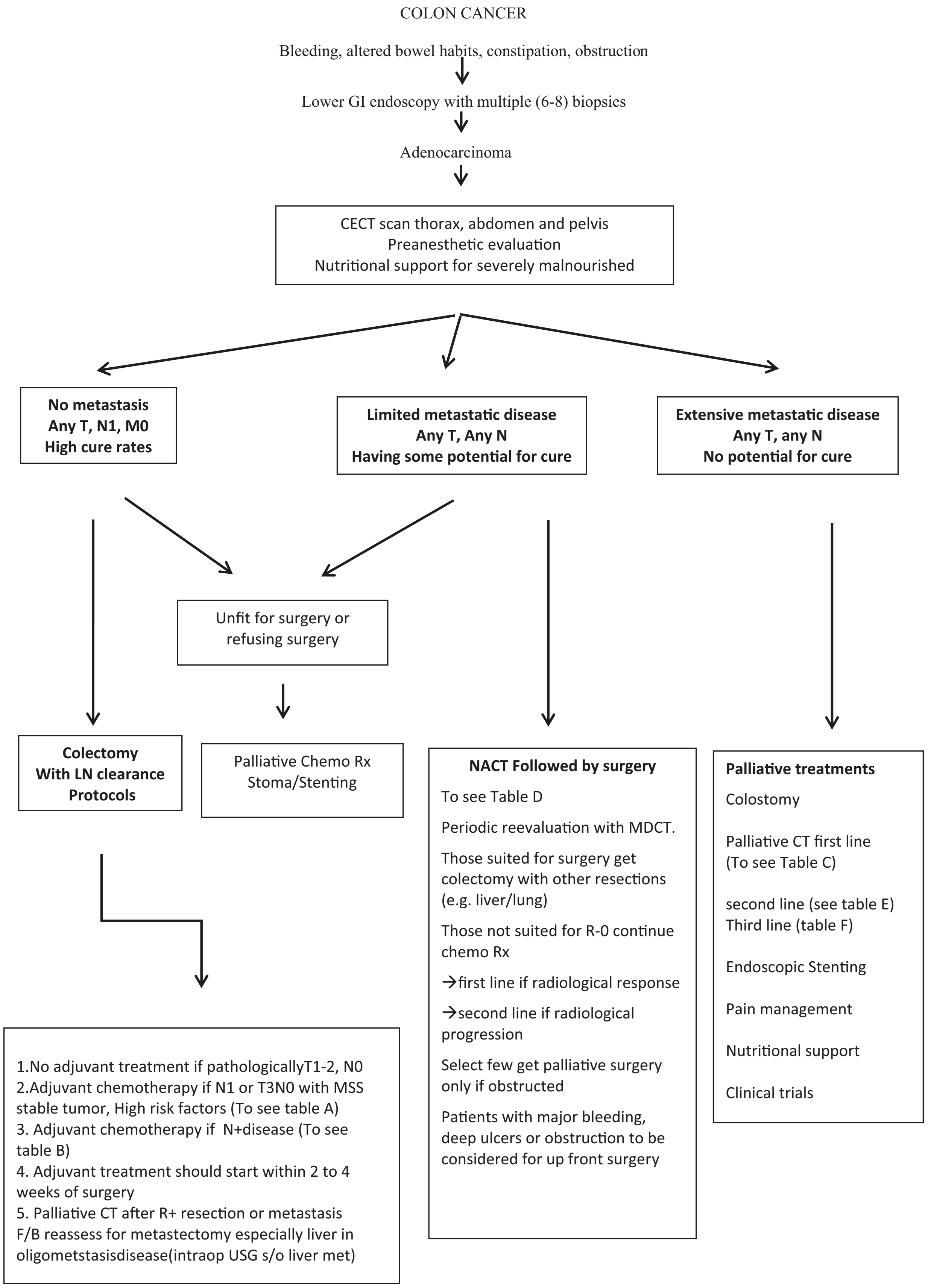
Stage	5-year survival rates [191] (%)
Stage I	92
Stage IIA	87
Stage IIB	65
Stage IIIA	90
Stage IIIB	72
Stage IIIC	53
Stage IV	12

12 Management of Recurrent Disease Including Specific Palliative Measures

Recurrent disease following radical colonic resection with or without adjuvant chemotherapy may be local or systemic. Metachronous distant metastasis is managed according to the principles of management for stage IV disease i.e. systemic chemotherapy with surgical resection if an R0 resection is feasible at all metastatic sites. Local recurrence may be nodal (most often at the root of the draining vascular pedicles of the resected primary) or luminal or both. Although systemic chemotherapy is essential in most cases of local recurrence, the best long-term outcomes are achieved only in cases where an R0 resection of the recurrent disease is achieved. Luminal recurrences can sometimes be resected R0 with multivisceral resections but large nodal recurrences at the root of the superior mesenteric artery are largely unresectable.

Bowel obstruction and intraluminal bleeding are probably the two most common presentations of recurrent colon cancer. For unresectable lesions, a diversion ileostomy or intestinal bypass offers good palliation of intestinal obstruction. However, in the presence of associated peritoneal disease, a careful evaluation of the level of obstruction and the number of points of obstruction is prudent before surgical exploration. Extensive peritoneal disease with an infiltrated small bowel mesentery and multi-level small bowel obstruction is generally not amenable to surgical palliation. Palliative radiotherapy plays an important role in symptomatic bone metastasis and may help decrease bleeding from unresectable lesions.

13 How We Do It at TMC (Fig. 5)



COLON CANCER

Bleeding, altered bowel habits, constipation, obstruction

Lower GI endoscopy with multiple (6-8) biopsies

Adenocarcinoma

CECT scan thorax, abdomen and pelvis
Preanesthetic evaluation
Nutritional support for severely malnourished

No metastasis
Any T, N1, M0
High cure rates

Limited metastatic disease
Any T, Any N
Having some potential for cure

Extensive metastatic disease
Any T, any N
No potential for cure

Unfit for surgery or refusing surgery

Colectomy
With LN clearance
Protocols

Palliative Chemo Rx
Stoma/Stenting

NACT Followed by surgery

To see Table D

Periodic reevaluation with MDCT.

Those suited for surgery get colectomy with other resections (e.g. liver/lung)

Those not suited for R-0 continue chemo Rx

→first line if radiological response

→second line if radiological progression

Select few get palliative surgery only if obstructed

Patients with major bleeding, deep ulcers or obstruction to be considered for up front surgery

Palliative treatments

Colostomy

Palliative CT first line
(To see Table C)

second line (see table E)
Third line (table F)

Endoscopic Stenting

Pain management

Nutritional support

Clinical trials

1.No adjuvant treatment if pathologicallyT1-2, N0
2.Adjuvant chemotherapy if N1 or T3N0 with MSS stable tumor, High risk factors (To see table A)
3. Adjuvant chemotherapy if N+disease (To see table B)
4. Adjuvant treatment should start within 2 to 4 weeks of surgery
5. Palliative CT after R+ resection or metastasis F/B reassess for metastectomy especially liver in oligometstasisdisease(intraop USG s/o liver met)

Fig. 5 How we do it at TMC

Table A

8 # of SA Cape/ Capox or 12 # 5FU Leco/ Folfox

Table B

8 # of Capox or 12 # Folfox

Table C

FOLFOX/FOLFIRI equivalent +/-Cetuximab/Panitumumab (ALL-RAS Wild) or Bevazucimab (ALL RAS Mutant) Folfoxiri + Bevacizumab (BRAF mutants)

Cape/ 5FU +/- Bevacizumab maintenance

CAPIRI +/- Bevacizumab[I]

Table D

Synchronous or staged colectomywith liver or lung resection: FOLFOX/CapeOx or Perioperative chemotherapy

FOLFIRI or FOLFOX or CapeOx± bevacizumaborFOLFIRI or FOLFOX ± Cetuximab (KRAS/NRAS wild-type [WT] gene only)followed by synchronous or staged colectomyand resection of metastatic disease

Colectomyfollowed by chemotherapy FOLFIRI or FOLFOX or CapeOX± bevacizumabor FOLFIRI or FOLFOX ± panitumumab or Cetuximab(KRAS/NRAS WT gene only)and staged resection of metastatic disease

Table E:

FOLFIRI ± bevacizumab or FOLFIRI ± ziv-aflibercept or

Irinotecan ± bevacizumab or Irinotecan ± ziv-aflibercept or

CAPIRI[J]

FOLFIRI + (cetuximab or panitumumab) (KRAS/NRAS WT gene only) or

(Cetuximab or panitumumab) (KRAS/NRAS WT gene only)+ irinotecan

Table F:

(cetuximab or panitumumab) (KRAS/NRAS WT gene only) or

(Cetuximab or panitumumab) (KRAS/NRAS WT gene only)+ SA irinotecan

Re challenge with CAPOX/ FOLFOX

Regorafenib

Cape MMC (investigational)

Oral metronomic chemotherapy (investigational)

When determining if adjuvant therapy should be administered, the following should be taken into consideration:

- Number of lymph nodes analyzed after surgery (<12)

Fig. 5 (continued)

- Poor prognostic features (eg, poorly differentiated histology [exclusive of those that are MSI-H]; lymphatic/vascular invasion; bowelobstruction; PNI; localized perforation; close, indeterminate, or positive margins)
- Assessment of other comorbidities and anticipated life expectancy.
- The benefit of adjuvant chemotherapy does not improve survival by more than 5%

Special situations: (MDT DECISION)

- Locally advanced colon cancer ,unresectable or requires multivisceral resection:
- Consider 6 weeks for NACT : CAPOX 2 #/ FOLFOX 3 # (FOXTROT TRIAL)

Fig. 5 (continued)

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Small Intestine Cancer

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Abbreviations

CAPOX	Capecitabine and oxaliplatin
DBE	Double balloon enteroscopy
EGD	Esophagogastroduodenoscopy
EGFR	Epidermal growth factor receptor
EUS	Endoscopic ultrasonography
FAP	Familial adenomatous polyposis
FU	Fluorouracil
GIST	Gastrointestinal stromal tumor
HNPCC	Hereditary nonpolyposis colorectal cancer
MMR	Mismatch repair
NCDB	National Cancer Database
NET	Neuroendocrine tumor
OS	Overall survival
PD	Pancreatoduodenectomy
SIA	Small intestinal adenocarcinoma
SIC	Small intestine cancer
TNM	Tumor, node, metastasis
VEGF	Vascular endothelial growth factor

1 Introduction

Small intestine contributes to 75% of the length of the gastrointestinal tract and 90% of its mucosal area; however, small intestine cancer (SIC) forms a small share (3%) of the entire gamut of gastrointestinal tract cancers [1]. Rarity of cancer development at this site can provide insights into presence of possible preventive mechanisms in this organ and anticancer strategies for more common malignancies at other sites. Adenocarcinoma of the small intestine is a rare malignancy. It is frequently diagnosed at advanced stage with either nodal or distant metastasis.

2 Epidemiology

Incidence of SICs in India appears to be extremely low, and no epidemiological studies have been published. Hospital-based data from India suggest that lymphomas of small bowel are more common than carcinomas [2]. Global incidence of SIC is less than 1.0 per 100,000 population [3]. Approximately 10,470 patients are diagnosed with and 1450 succumb to SIC every year in the United States [1, 4]. It accounts for only 0.42% of total cancer cases and 2.3% of cancers of digestive system in the United States. It is more common in North America and Europe than Asia [5]. SIC is usually seen in the sixth and seventh decades of life [2]. SIC is more common in men compared to women [4].

3 Histology

More than 40 histological types of small bowel tumors are known [6]. Adenocarcinoma (36.9%), carcinoid (37.4%), lymphoma (17.3%) and gastrointestinal stromal tumor (GIST) (8.4%) are four commonly found primary small bowel tumors (Table 1) [7]. Adenocarcinomas are seen more frequently in duodenum; NETs often develop in ileum while lymphomas tend to occur in jejunum. In the past few decades, incidence of small bowel neuroendocrine tumor (NET) has surpassed that of adenocarcinomas of small bowel [8, 9]. Benign tumors such as adenomas, lipomas and hemangiomas also occur in the small bowel. The focus of this chapter is on management of small intestinal adenocarcinoma (SIA).

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Table 1 A few important histological types of small intestinal tumors (WHO classification) [5]

Epithelial tumors **Adenoma** **Intraepithelial neoplasia (dysplasia)**
Carcinoma • Adenocarcinoma • Mucinous adenocarcinoma • Signet-ring cell carcinoma • Small cell carcinoma
Carcinoid (well-differentiated endocrine neoplasm) **Nonepithelial tumors** • Lipoma • Leiomyoma • Gastrointestinal stromal tumor • Leiomyosarcoma
Malignant lymphomas **Metastasis** **Polyps** • Hyperplastic (metaplastic) • Peutz–Jeghers

4 Etiopathogenesis

Faster transit time compared to colon and rectum, relatively diluted liquid contents, higher amount of lymphoid tissue in small intestinal wall and rapid turnover of cells are few hypotheses proposed to explain low incidence of cancer at this site. Various risk factors and predisposing conditions are known to be responsible for causation of SIC. Many SIAs develop from adenomas through adenoma–carcinoma multistep sequence involving multiple specific genetic changes at each step, similar to colorectal adenocarcinoma [10]. Size and histology of the adenomas influence the risk of progression to adenocarcinoma. Larger size and villous adenomas carry higher risk for progression. Molecular biology of SIA and colorectal adenocarcinomas shows similarity [11]. DNA mismatch repair (MMR) pathway alterations are also frequently found in SIAs similar to colorectal adenocarcinomas. A high percentage of SIAs also exhibit epidermal growth factor receptors (EGFR) and vascular endothelial growth factor (VEGF) receptors, suggesting that therapeutic strategies targeting them may be useful in SIAs [12].

4.1 Hereditary Cancer Syndromes, Predisposing Conditions and SIA [13] (Table 2)

4.1.1 Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Syndrome

Germline mutations in DNA mismatch repair genes are responsible for causation of HNPCC. Patients have increased risk of developing colorectal cancer as well as cancers of other organs like small intestine and endometrium. The risk for SIA has been reported to be higher in MLH1 mutation carriers [90]. HNPCC-associated SIAs occur at an earlier age and appear to have a better prognosis than those occurring in the general population [14].

Table 2 Risk factors for small intestine cancer

Hereditary syndromes • HNPCC (hereditary nonpolyposis cancer colon syndrome) • Familial adenomatous polyposis • Peutz–Jeghers syndrome • Cystic fibrosis
Inflammatory conditions • Crohn's disease • HIV infection • Coeliac disease **Lifestyle-related factors** • Tobacco usage • Smoking • High intake of red meat and smoked food **Previous surgery-related factors** • Ileostomy • Pouches • Conduits • Biliary diversion

4.1.2 Peutz–Jeghers Syndrome

The syndrome is characterized by hamartomatous polyps in gastrointestinal tract. Patients with Peutz–Jeghers syndrome are at increased risk of small bowel, other gastrointestinal, breast, ovarian, uterine cervical, ovarian, testicular and lung cancers [15].

4.1.3 Familial Adenomatous Polyposis (FAP) Syndrome

FAP syndrome is caused by germline mutation in APC gene. Patients develop colonic and duodenal adenomatous polyps and have increased risk of adenocarcinoma development. Fifty to 90% of patients with FAP develop duodenal adenomatosis, and 3–5% of these patients develop duodenal cancer. Risk of malignant transformation is higher with periampullary adenomas [16, 17].

4.2 Inflammatory Bowel Disease and Chronic Inflammation

Small intestinal Crohn's disease predisposes to adenocarcinoma. Relative risk is reported to be as high as 60. Extended duration of the disease, distal jejunal and ileal location, male sex, small bowel bypass loops, strictures, chronic fistulous disease, young age at diagnosis and occupational hazards (aromatic compounds, asbestos and solvents) are suggested to be associated with an increased risk of small bowel carcinoma in patients with Crohn's disease [13]. There is a proportionate increase in risk with increase in extent as well as duration of small bowel involvement. Celiac disease is an inflammatory small intestinal disorder characterized by the inability of the small intestine to deal with the gluten fractions of cereals. Celiac disease increases risk of SIA as well as small bowel lymphoma. Similar to Crohn's disease, relative risk is reported to be as high as 60 to 80. SIAs associated with celiac disease are most often located in the jejunum and are more likely to develop as an adenoma–carcinoma sequence than as dysplasia in flat mucosa [18].

4.3 Other Associations

Radiation exposure and cystic fibrosis also seem to be involved in causation in some cases.

Tobacco usage, smoking, high intake of red meat and smoked food are associated with SIA [19]. Ileostomy, pouches, conduits and biliary diversion increase the risk of SIA [20].

5 Clinical Presentation

In early stages, adenocarcinoma of the small intestine is usually asymptomatic. Most patients present with symptomatic lesions during the sixth and seventh decades of life. Age of presentation is usually 10 years earlier than average age for sporadic cases and for tumors arising in individuals with genetic or familial predisposition [14, 21]. Symptoms are vague which results in late of detection of these cancers. Symptoms may include nausea, vomiting, abdominal pain, constipation, malaise, weight loss, anemia and diarrhea. Usually patients develop symptoms when tumor grows large and obstructs the small intestine or compresses on adjacent structures. Approximately 77% of small bowel cancers present with intestinal obstruction or peritonitis due to bowel perforation [14]. Occult blood in stools or hematochezia can be the manifestations of SIC. Few small intestinal tumors may be detected incidentally or may present as an innocuous primary with distant visceral metastasis especially in case of neuroendocrine tumors (NET).

6 Evaluation and Work-Up

Long length and anatomy of small intestine make diagnosis of small bowel neoplasms difficult and challenging. Small intestinal cancer distal to the duodenum is relatively inaccessible. Definitive preoperative diagnosis is made in up to 30–40% patients.

Esophagogastroduodenoscopy (EGD) is useful in identifying and sampling duodenal lesions. Push and pull enteroscopy (double balloon enteroscopy) and capsule endoscopy are two diagnostic tools with potential to locate the site of primary in jejunum or ileum. The accuracy rates of double balloon enteroscopy (DBE) ranges from 94% to 100% depending on the histology [22]. Push–pull enteroscopy has capability of therapeutic intervention but also needs greater expertise and anesthesia [23].

CT scan and MRI usually help to locate distant and nodal metastasis but have a low sensitivity to identify the primary. The benefit of CT scan over conventional imaging methods of small bowel enteroclysis or barium small bowel follow through is demonstration of both intraluminal as well extraluminal features related to the tumor. Duodenal lesions are usually seen as intraluminal polypoidal lesions on cross-sectional imaging while distal polypoidal lesions may cause intussusception and generate a characteristic "target sign." Adenocarcinomas are seen as tumor mass with annular luminal narrowing and irregular edges. CT enteroclysis with high volume neutral oral contrast or direct infusion of contrast into the small bowel helps in improving sensitivity of tumor localization [24].

7 Staging

Small intestine cancer is staged as per the AJCC—tumor, node, metastasis (TNM) cancer staging system. Depth of tumor invasion determines the T stage where T1 refers to tumor infiltration up to submucosa and T4 implies adjacent organ infiltration. Stage groupings are similar to colonic cancer staging. Node-negative T1, T2 disease implies Stage 1, and T3, T4 is a stage II disease. Node-positive disease determines Stage III, and distant metastasis is a stage IV disease [25].

8 Management

8.1 Surgical Management of SIA

Management usually is dictated by the histology of the neoplasm. Resection is definitive treatment for most small bowel neoplasms. Surgery involves excision of tumor with at least 5 cm margins on each side of the bowel and mesentery to clear the draining lymph nodes till the base of supplying mesenteric vessel. Simple excision suffices for benign tumors of small intestine.

8.1.1 Duodenal Adenocarcinomas

Duodenal adenocarcinomas involving the ampulla usually warrant a pancreatoduodenectomy (PD) for radical excision of the tumor. Ampullary resection, i.e., ampullectomy, may suffice for ampullary adenomas or early ampullary adenocarcinomas. Ampullectomy can be considered in benign lesions smaller than 3 cm, small neuroendocrine tumors and T1 well-differentiated carcinomas of the ampulla [26, 27].

Ampullary resections can be accomplished by endoscopy guidance or transduodenal surgical approach [28, 29]. Clinical judgment, endoscopic ultrasonography (EUS) and intraoperative pathological confirmation are helpful in determining adequacy of resection [19]. It has been noticed that tumor with characteristics of protruded adenoma or well-differentiated adenocarcinoma, no duodenal invasion as determined by endoscopic ultrasonography, no pancreatic ductal infiltration as determined by intraductal ultrasound and diameter of the pancreatic duct ≤3 mm determined by endoscopic retrograde cholangiopancreatography had no lymph node metastasis [30]. Such tumors seem to be ideal candidates for curative ampullary resection. Compliance to surveillance protocol is important and a must after ampullary resection as it is associated with higher rate of recurrence [31, 32]. Pancreas preserving duodenectomy with lateral duodenojejunostomy may be required for lesions of third and fourth parts of duodenum [33]. Some superficial nonampullary duodenal tumors (localized to mucosa and submucosa), which are not feasible for endoscopic resection, may be amenable to transduodenal excision and local full thickness resection. This can also be accomplished by minimally invasive technique with combination of laparoscopy and endoscopy in selected cases [34]. These surgical modalities help to obviate the need of PD or pancreas preserving duodenectomy. This should be attempted in clinicoradiologically node-negative cases or in patients with low risk of nodal metastasis [26]. PD does not confer survival advantage compared with segmental resection as per various retrospective studies [35, 36]. A large series from Mayo clinic did not demonstrate any statistically significant difference in terms of 5-year overall survival (OS), rate of R0 resection or local recurrence between pancreatoduodenectomy or total pancreatectomy versus segmental resection or transduodenal excision of duodenal tumors [37]. There was no significant difference between the two groups in terms of 5-year overall survival (52% vs. 61%), rate of margin negative resections or local recurrence rates.

8.1.2 Jejunal and Ileal Adenocarcinomas

Patients with these lesions may present with intestinal obstruction or melena necessitating emergency surgery. Optimization of these patients before embarking on surgery should be performed. En bloc resection of involved segment and mesentery with adequate margins is needed. Terminal ileal lesions may necessitate a radical right hemicolectomy.

8.2 Adjuvant Chemotherapy for Small Bowel Adenocarcinomas

There is a dearth of prospective trials evaluating the role of adjuvant chemotherapy post resection of SIAs. Evidence for adjuvant chemotherapy for small intestinal adenocarcinomas exists in the form of retrospective studies and is mainly 5-fluorouracil based.

Regimen containing oxaliplatin plus short-term infusional fluorouracil (FU) and leucovorin is usually selected based on the MOSAIC trial that proved it to be superior to FU and leucovorin alone in patients with colon cancer [38]. Survival advantage with adjuvant chemotherapy compared to surgery alone was seen in a propensity score-matched analysis of data from the National Cancer Database (NCDB) [39]. Use of adjuvant chemotherapy in small bowel adenocarcinoma is based upon the patterns of recurrence and an extrapolation from evidence showing its survival benefit in node-positive colon cancer cases.

8.3 Management of Metastatic Disease

Role of surgery in metastatic disease is mainly to palliate bleeding, obstruction or perforation. Resection may be warranted in case of bleeding or perforation in primary tumors. Intestinal bypass surgery may be helpful to maintain oral intake of food and improve symptoms and quality of life in patients with obstructed primaries. Mainstay of treatment in this scenario is palliative chemotherapy. Palliative chemotherapy compared to best supportive care provided a survival benefit in multiple retrospective studies [40]. The various regimens being studied in phase II trials include combination of capecitabine and oxaliplatin (CAPOX) with bevacizumab, CAPOX with panitumumab and Nab-paclitaxel [41].

9 Prognosis

As majority of cases are diagnosed in advanced stage, prognosis is usually poor. Five-year disease-specific survival was 65% for stage I, 48% for stage II, 35% for stage III and 4% for stage IV disease [34]. Poor prognostic features include old age (>55 years), T4 tumor, lymph node involvement, duodenal followed by ileal primary and positive margins [42, 43].

10 How We Do It at TMC (Table 3)

In our experience, oncologic small bowel resections were more commonly performed for lymphomas and non-SIA pathologies in TMC than for adenocarcinomas.

A multidisciplinary team consisting of surgical oncologist, medical oncologist, radiotherapist, pathologist, radiologist, interventional radiologist and palliative care specialists is involved in treatment planning in elective presentations. High-risk patients are discussed with the team of anesthesi-

Table 3 Summary

- SIAs are rare and comprise approximately one-third of small intestinal malignancies.
- Hereditary cancer syndromes, chronic inflammatory conditions of the bowel and particular lifestyle-related factors are implicated in causation.
- Presentation is usually delayed and vague or sometimes acute due to complications of intestinal obstruction or melena.
- Diagnosis is usually by endoscopy for duodenal lesions and cross-sectional imaging for distal lesions.
- Radical resection is the only curative therapy.
- Adjuvant chemotherapy regimens are analogous to colon cancer.
- Obstruction, bleeding and/or perforation in advanced stages can be palliated by surgery.
- Palliative chemotherapy helps improve survival in metastatic disease.

ologist by surgical team before all major elective procedures, and decisions regarding adjuvant therapy are also planned in a similar multidisciplinary clinic. A personalized management plan is offered after taking into consideration the patient-related factors, disease-related factors and the logistics. The treatment plan is conveyed to and discussed with the patient and relatives after such clinic by the primary surgical team, and patients are guided to the appropriate specialists.

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Anal Canal Cancer

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Abbreviations

APR	Abdominoperineal resection
CMT	Combined modality treatment
EORTC	European Organization for Research and Treatment of Cancer
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
IMRT	Intensity-modulated radiotherapy
MRI	Magnetic resonance imaging
RCT	Randomized controlled trials
RT	Radiotherapy
TNM	Tumor node metastases
UKCCCR	United Kingdom Coordinating Committee for Cancer Research

1 Introduction

Anal canal cancer is a rare gastrointestinal malignancy accounting for 1–6% of anorectal neoplasms [1]. Over the decades, the treatment for anal canal cancer has transitioned from surgery to sequential treatment (chemotherapy, chemoradiation, surgery) to definitive chemoradiation alone. Chemoradiation is the standard of care despite absence of randomized trials comparing it with surgery [2]. This is one of the few cancers which exemplify organ preservation achieved with definitive radiotherapy.

Anal canal is the distal part of the gastrointestinal tract and measures about 3–4 cm in length [3]. Dentate or pectinate line is an important landmark, where the glandular mucosa transitions to squamous mucosa. A zone of transitional epithelium may be present just proximal to dentate line. Anal canal extends from the anorectal ring (puborectalis muscle sling or 1–2 cm proximal to dentate line) to the anal verge. Anal verge is a mucocutaneous junction defined at the point at which the nonkeratinizing squamous epithelium lining the anal canal merges with the perianal skin. Other landmarks are outer edge of the internal anal sphincter and the palpable intersphincteric groove. The wall of anal canal is composed of internal and external sphincter muscles. The internal sphincter is the distal continuation of the inner circular muscular layer of rectum while the external sphincter is composed of levator ani, puborectalis sling and the external sphincter muscle. Anal canal is lined by three different histologies namely glandular and transitional in the proximal portion (above dentate line) and squamous in the distal portion [4]. Anal margin is a separate entity and is defined as the area extending up to 5 cm from the anal verge. Perianal cancers are defined as tumors that arise within the skin at or distal to the squamous mucocutaneous junction, can be seen entirely with gentle traction on the buttocks and are within 5 cm of the anus as per the American Joint Committee on Cancer (AJCC) eighth edition [5]. Dentate line acts as the watershed for lymphatic drainage. Tumors above the dentate line drain to mesorectal and internal iliac nodes while those below it, drain to the superficial and deep inguinal nodes and femoral nodes.

2 Incidence and Epidemiology in India and Global

Anal canal cancers account for 2% of all gastrointestinal cancers [1]. The age-standardized incidence rate of anal canal cancer is around 1 to 2 per 100,000 per year. The inci-

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dence is rising worldwide over the years at the rate of 1–3% per year [6]. Islami et al. evaluated the international trends in anal canal cancer [7]. They noted an increase in incidence in mainly developed high-income countries, while in the Asian countries and Spain, the incidence was low and incidence remained unchanged. The reasons for the rise are related to sexual behavior, human immunodeficiency virus (HIV) infection, immunosuppression and high incidence and persistence of human papilloma virus (HPV) infection [8]. In the United States, about 8600 cases are diagnosed annually and account for 0.5% of all cancers [9].

In India, anal canal cancer is uncommon. Takiar et al. estimated the total number of cancer cases in India from 2010 to 2020 [10]. The estimated cases of anal canal cancer were 3500 in 2010, 3750 in 2015 and 4083 by 2020. There was higher incidence in males compared to female. As per GLOBOCAN 2018, anal canal cancers account for 0.5% of all new cases and 0.5% of mortality due to cancer. The total number of new cases amounts to 4895 with a cumulative risk of 0.04% [11].

2.1 Risk Factors

Historically, chronic inflammation due to hemorrhoids, fissure or inflammatory bowel disease was thought to be causative for anal canal cancer [12]. This has been disproved by various large cohort studies [13, 14]. The established risk factors for anal canal cancer are HPV, HIV, anal receptive intercourse, multiple sexual partners, exposure to sexually transmitted diseases, smoking, immunosuppression and prior history of preinvasive or invasive cervical, vaginal or vulval cancer. There is a higher preponderance among men. However, incidence among women is increasing due to HPV.

2.2 HPV

HPV is the most common sexually transmitted disease worldwide and is the main causative risk factor for anal cancer. A strong association has been seen between HPV and malignancies of cervix, vulva and anal canal. Over 90% of cases of anal canal cancer are associated with HPV and HPV DNA has been isolated from tissue [15]. The most common subtype seen in anal cancer is HPV 16 [16]. P16 is a surrogate marker for HPV 16 and can be readily identified on immunohistochemistry. HPV is also associated with precursor lesions and in men who have sex with men (MSM).

2.3 HIV

The HIV-positive individuals have two-fold higher risk of anal canal cancer especially among MSM [17]. Despite highly active antiretroviral therapy (HAART), the incidence has increased [18]. In HPV-positive individuals, coexistent HIV infection further increases the risk of precursor anal lesions and anal canal cancer and time afforded by treatment may allow these lesions to progress to malignancy [19]. The causative mechanism of HIV in anal canal cancer is not clear. It is plausible that HIV interacts with HPV leading to higher prevalence of HPV, HPV replication and persistence in HIV-infected individuals. Immunosuppression due to HIV may be contributory factor as well.

2.4 Sexual Activity

Receptive anal intercourse is a strong risk factor with a relative risk of over 30. The highest incidence is seen in MSM with HIV and HPV co infection [20]. Multiple sexual partners, history of genital warts, history of sexually transmitted disease like chlamydia trachomatis or gonorrhea are risk factor for anal cancer in both sexes [21]. A history of cervical dysplasia or cervical cancer also increases the risk for anal cancer possibly due to HPV infection [22].

2.5 Smoking

Smoking increases the risk of anal canal cancer (relative risk 2–5) and acts as a cocarcinogen for cervical cancer [23, 24].

2.6 Chronic Immunosuppression

Immunosuppression in patients with solid organ transplant and autoimmune disease (on steroids) is associated with high risk of anal canal cancer. This could be related to increased risk of HPV infection and persistence due to impaired ability of the body to clear HPV.

3 Clinical Presentation in India and Global

Anal canal cancer is commonly seen in older adults with a peak age of presentation between 60 and 65 years [25]. Women are more commonly affected. The diagnosis of anal canal cancer is often delayed as symptoms are commonly attributed to hemorrhoids or fissure in ano [26]. The most common symptom of presentation is bleeding per rectum which is seen in over 45–50% of the patients [25]. Other symptoms are pain, mass per rectum, mass in inguinal region (about 30%). The tumor may extend to the rectum or perianal skin. About 20% of patients may not have any symptom. A history of anal warts may be present in 30–50% of the cases. As per the SEER database, 50% have localized disease in the anus, 30% present with lymphadenopathy, 12% have metastatic disease and another 8% have unknown stage [27].

In India, men are more commonly affected than women [28]. Advanced disease at presentation is seen in over 45% of cases [29]. Patients present with large primary associated with ulceration, fungation, abscess or multiple fistulas in the perianal region. Invasion of rectovaginal septum in women and prostate or urethra in men may be seen in about 10%.

4 Evaluation and Work-Up

The clinical staging includes a detailed history and physical examination, pathological confirmation and imaging. A detailed digital rectal examination is a mandate and documentation of the craniocaudal extent, circumferential extent, involvement of rectum, anal sphincter tone should be done. A gynecological exam including cervical cancer screening is recommended. Clinical palpation of bilateral inguinal nodes should be performed, and fine needle aspiration of suspicious nodes should be done. Routine blood investigations (which includes complete blood picture, renal and liver functions tests) along with HIV testing should be carried out. In HIV-positive patients, CD4 count should be measured and HAART should be started.

Proctoscopy and biopsy with histological analysis are done to confirm the diagnosis. The most common histology is squamous cell carcinoma in over 80% [30]. Other histologies are basaloid, cloacogenic or transitional or adenosquamous [31]. Epidermoid carcinoma is a collective term used for all these histologies. Adenocarcinoma or melanoma is rare. Adenocarcinomas are managed as primary rectal cancers. The *Histological classification* of anal canal cancer is shown in Table 1.

Table 1 Histological classification

Histology
Squamous cell carcinoma • Large cell keratinizing • Nonkeratinizing (transitional) • Basaloid
Adenocarcinoma
Small cell carcinoma
Undifferentiated carcinoma
Others: • Sarcoma • Lymphoma • Melanoma

The extent of local and nodal disease is assessed by imaging. An accurate assessment of primary in terms of size and extent is required for staging. Magnetic resonance imaging (MRI) is the modality of choice to characterize the locoregional spread. The primary has low to intermediate signal relative to muscle on T1 weighted images and is hyperintense on T2 weighted images. The nodes have signal similar to primary. The tumor size, circumferential extent, invasion of adjacent organs (vagina, urethra, prostate and bladder), extension to ischioanal or ischiorectal fossa and presence of fistula should be documented. The sensitivity of MRI for local staging is 90–100% [32]. CT thorax and abdomen is usually performed to exclude distant metastases mainly in lung and liver. Distant metastasis at presentation is uncommon (9–20%). PET CT has shown encouraging results with upstaging of the disease in 17% of the cases and in 29% cases the management was altered [33]. Over 98% of anal cancers are FDG avid and PET has high sensitivity (89–98%). However, it is still considered investigational and not routinely practiced. It has a role in recurrent setting for staging especially when salvage surgery is planned. The routine follow-up posttreatment with PET-CT is not warranted [34]. The staging is performed with tumor node metastases (TNM) staging system and the eighth edition is currently used. The perianal cancers are staged and treated as anal canal cancer. Staging can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 282, Chapter no. 21, Anus, Table: Definition of TNM and AJCC Prognostic Stage Groups which can be accessed at https://emedicine.medscape.com/article/2003634-overview

5 Principles of Management

Multimodality treatment approach is standard. Definitive radiation is the standard treatment for all stages. Chemotherapy is used in locally advanced cases along with radiation while in metastatic scenario, it is the sole treatment. Surgery is reserved for salvage post radiation and in early anal margin cancers.

5.1 Radiation Management

5.1.1 Evidence

Radiation is the principal modality of treatment in localized anal canal cancer due to its sphincter preserving and colostomy avoiding potential with superior oncological results. Nigro et al. were the first to explore chemoradiation in anal canal cancer with the intention of improving control rates with surgery alone [35]. Since squamous cell cancers are sensitive to radiation and chemotherapy acts as a radiosensitizer, the addition of chemoradiation prior to surgery was tested. The original Nigro's protocol consisted of a low dose of radiation (30 Gy in 15 fractions over 3 weeks) along with Mitomycin 0.5 mg/kg on day 1 and 5 Fluorouracil (5-FU) 25 mg/kg day 1–5 continuous infusion. The preliminary report of this regimen in three patients published in 1974 showed a complete clinical response (CR) in all three patients and a pathological CR in two patients (1 patient refused surgery) [35]. In an updated series of 45 patients, Leichman showed that 84% (*n* = 34) of patients had CR with chemoradiation alone and surgery was deemed unnecessary in this cohort [36]. Surgery was done only in case of residual tumor. The 5-year overall survival was 67%, and colostomy-free survival was 59%. This paved the way for practice change leading to acceptance of chemoradiation as the standard treatment even in the absence of a prospective randomized trial comparing surgery with chemoradiation.

These reports were further evaluated and confirmed by other investigators at different institutions with radical radiation doses (40–60 Gy) and different schedules (continuous and split course) [37–40]. Some studies showed good local control rates and survival outcomes with radiotherapy alone [41, 42]. The need for concurrent chemotherapy was questioned and there were concerns regarding increase in acute and late toxicity with concurrent chemotherapy.

Two large randomized controlled trials (RCT) compared radiation alone with chemoradiation. The United Kingdom Coordinating Committee for Cancer Research (UKCCCR) conducted a multicentric RCT in 585 patients of ACC (anal cancer trial ACT I) T1–T4 stage from 1987 to 1994 comparing 290 patients treated with radiation alone with 295 patients treated with combined modality treatment (CMT) [43]. Radiotherapy (RT) was delivered to a dose of 45 Gy in 20 to 25 fractions over 5 weeks in both arms. Chemotherapy consisted of 5FU (1000 mg/m^2 over 4 days or 750 mg/m^2 over 5 days in week 1 and 5 of radiation) and mitomycin (12 mg/m^2 bolus on day 1, single dose) in CMT arm. Response assessment was done at 6 weeks after treatment. Further radiotherapy boost (brachytherapy 25 Gy with iridium implant or external beam boost of 15 Gy/6 fractions) was considered in patients with good response (≥ 50% regression), while salvage surgery was done in poor responders. Local failure rate was the primary endpoint of the trial. At a median follow-up of 42 months, the CMT arm had significantly lower failure rates compared to RT alone (36% vs. 59%, $p < 0.0001$) with a 46% risk reduction. Overall survival was similar in both arms; however, deaths from ACC were reduced in CMT arm ($p = 0.02$). Acute toxicity was higher in CMT arm ($p = 0.03$).

A 13-year update from ACT 1 trial showed 25% reduction in risk of locoregional failure with CMT (32% vs. 54%, $p = < 0.01$) [44]. There was 12.5% reduction in risk of death from ACC in CMT arm. Median survival was 7.6 years with CMT vs. 5.4 years with RT alone. Noncancer deaths were higher in CMT arm and were predominantly due to cardiovascular cause, treatment related or pulmonary in first 5 years while due to secondary malignancy beyond 5 years. Lung cancer was the most common second malignancy, likely due to common risk factor of smoking. Early increase in noncancer deaths in CMT arm could be the reason for lack of survival advantage.

European Organization for Research and Treatment of Cancer (EORTC) conducted a RCT in 110 T2–T4 N0–3 or T1–2 N+ ACC patients from 1987 to 1994 comparing RT alone with CMT [45]. RT was delivered to a dose of 45 Gy in 25 fractions over 5 weeks in both arms. Chemotherapy consisted of 5FU (750 mg/m^2 over 5 days in weeks 1 and 5 of radiation) and mitomycin (15 mg/m^2 bolus on day 1, single dose) in CMT arm. Response assessment was done at 6 weeks after treatment. Boost of 15 Gy was given good responders while 20 Gy in poor responders. Surgery was done in case of stable disease or progression. Clinical CR was increased in CMT (80%). At 5 years, there was significant improvement in locoregional control rate by 18% ($p = 0.02$), colostomy-free survival by 32% ($p = 0.002$) and event-free survival ($p = 0.03$) with CMT. No difference in toxicities and overall survival between the arms.

These two trials have established chemoradiation as standard of care in localized ACC. Though there was no survival advantage, locoregional rates were superior with chemoradiation albeit with higher toxicity.

Conformal external beam radiotherapy should be used to get good target coverage and avoid the organ at risk. Intensity-modulated radiotherapy (IMRT) is preferred modality of treatment technique. Kachnic et al. evaluated the role of dose painted IMRT in anal canal cancers with the aim of reducing acute grade 2 or higher combined gastrointestinal and genitourinary toxicity (RTOG 0529) [46]. They showed significant reduction in acute grade 2+ hematologic and grade 3+ dermatologic and gastrointestinal toxicity. However, the primary endpoint was not met. On a follow-up of 8 years, the update by Kachnic et al. showed that the late effects were mainly grade 2–3 and lower compared to previous series (18% grade 1, 55% grade 2, 16% grade 3, 0% grade 4, 2% grade 5 (sinus bradycardia)) [47]. The outcomes were similar to historical cohort of RTOG 9811 with 5-year locoregional failure of 16%, disease-free survival (DFS) 68% and OS 76%.

5.2 Radiation Planning

The patients are positioned in supine position. To minimize skin folds, immobilization of legs in frog-leg position can be done. Markers should be placed at anal verge and on palpable or biopsy-proven adenopathy to avoid the risk of geographic miss. The target volumes include the gross disease (primary and nodes), a margin of 2–2.5 cm around the primary, entire mesorectum with perirectal lymph nodes and the elective lymph node volumes (bilateral inguinal, internal iliac and external iliac). The total dose prescribed varies according stage. T1–2 N0 tumors are treated to a dose of 50.4 Gy in 28 fractions at 1.8 Gy per fraction. T3–4 require a higher dose to about 54 Gy in 30 fractions at 1.8 Gy per fraction. Positive nodes are boosted to 54–55 Gy. In case of poor response at the completion of External Beam Radiotherapy (EBRT), further 5–10 Gy boost may be considered with either external beam or brachytherapy [28].

In case of metastatic setting, poor performance status or elderly (not fit for chemotherapy), shorter hypo fractionated schedules (40 Gy/15 fractions, 30 Gy/10 fractions or 20 Gy/5 fractions) may be considered for symptom and local control.

5.3 Response Assessment

Response to chemoradiation is assessed at 6–8 weeks after chemoradiation. If there is partial response or stable disease, patients are kept on follow-up till 6 months after completion of treatment [48]. If there is any progression posttreatment or up to 6 months, patients should be considered for biopsy. MRI is done to evaluate local extent of disease and suitability for surgical salvage. CECT thorax abdomen or Positron Emission Tomography-Computed Tomography scan (PET-CT) is done to rule out distant metastases. Biopsy is contraindicated in case of complete response. Biopsy of the irradiated tissues may lead persistent nonhealing ulceration due to poor vascularity and may lead to necrosis. Biopsy should be done only in the case of strong clinical suspicion of recurrence (proliferative growth or ulceration). If proven positive, MRI pelvis for local disease extent and CECT thorax abdomen or PET-CT should be done to rule out distant metastases.

5.4 Follow-Up

Follow-up is essentially clinical. Patients are followed up every 3 months for up to 2 years and every 6 months for up to 5 years and annually thereafter. At each visit, a clinical examination which includes digital rectal examination and palpation of bilateral inguinal nodal regions should be done. Fibrosis and stenosis of anal canal post radiation may preclude complete clinical examination. Imaging with MRI may be considered to detect local recurrences. Majority of the recurrences are locoregional and occur within 2 years. Long-term update of ACT-1 trial showed that beyond 5 years less than 2% of patients develop a locoregional relapse [44]. Distant metastases alone (without locoregional relapse) occurred in only 7%. Hence during follow-up, attention should be paid to detect early recurrences and complications of chemoradiation.

5.5 Complications

The most common acute complications are dermatitis, gastrointestinal (diarrhea and stomatitis), hematologic (anemia, leucopenia) and genitourinary. With IMRT the toxicity is less. The rates of acute toxicity were grade 2+ hematologic, 73%; grade 3+ gastrointestinal, 21%; and grade 3+ dermatologic, 23%. The late complications are diarrhea, proctitis and rarely anal stricture or incontinence. With IMRT the risk of late toxicity grade 3 and higher is 16%.

6 Chemotherapy Management

6.1 Evidence

6.1.1 Nonmetastatic Disease

Chemotherapy plays an important role in multimodality treatment. Although their concurrent role is well established, neoadjuvant and maintenance chemotherapy failed to show any benefit.

6.1.2 Concurrent Chemotherapy

The two RCTs (EORTC and UKCCCR ACT-1 trials) have shown the superiority of chemoradiation. The better local control and colostomy-free survival came at the cost of higher acute toxicity in the form of moist desquamation, diarrhea and hematologic toxicity. The overall acute toxicity in CMT arm of ACT-1 trial was 47% (140/292) compared to 39% with RT alone [43]. Severe skin, gastrointestinal and genitourinary reactions were seen in 35%, 10% and 2%, respectively, in CMT arm. Considering the toxicity profile of Mitomycin C, its efficacy and role in CMT was questioned. Nonrandomized studies showed improved outcome with addition of mitomycin compared to 5FU alone [49]. This was addressed by a randomized trial conducted by Flam et al. [50]. The Radiation Therapy Oncology group (RTOG) 8704 compared the addition of Mitomycisn to 5FU versus 5FU alone along with radiation in 310 patients of ACC. Radiation dose in both arms was 45 Gy in 25 fractions with boost up to 50.4 Gy to primary and positive nodes. 5FU was in both arms was administered at 1000 mg/m^2 continuous infusion for 4 days on day 1 and day 28 of RT. Mitomycin was administered at 10 mg/m^2 bolus on day 1 and day 28 of RT. Response assessment was done at 4 to 6 weeks after RT and those with a positive biopsy of residual disease received salvage treatment with chemoradiation (RT boost of 9 Gy/5 fractions along with cisplatin and 5FU). At 4 years, the addition of mitomycin improved disease-free survival (73% vs. 51%, $p = 0.0003$), colostomy rate (9% vs. 22%, $p = 0.002$), colostomy-free survival (71% vs. 59%; $p = 0.014$) and local-regional recurrence rates (17% vs. 36%, $p < 0.001$). No difference in overall survival was seen. The main toxicities were hematologic, dermatologic and gastrointestinal. Overall acute grade 4 toxicity was higher with mitomycin (23% vs. 7%).

Despite good results with MMC, over 30% of patients still had local relapse and about 40% experience distant relapse [43]. The combination of 5FU and MMC in Nigro's protocol was empirical. Cisplatin is one of the most active agents for squamous cell cancer. It has synergism with both RT and 5FU and would serve as an effective less toxic alternative to MMC. This was tested in few phase II trials which showed encouraging results in terms of response rates and toxicity [51–53]. ACT II trial assessed the efficacy of cisplatin–5FU combination over 5FU–MMC in an RCT in terms of complete response and toxicity [54]. In this 2 × 2 factorial trial, 940 ACC patients of all stages were accrued. Apart from randomization of MMC vs. Cisplatin, patients underwent a second randomization for maintenance chemotherapy. Radiation dose was 50.4 Gy in 28 fractions over 5.5 weeks in both arms. 5FU in both arms was administered at 1000 mg/m^2 continuous infusion for 4 days on day 1 and day 29 of RT. Mitomycin was administered at 12 mg/m^2 bolus on day 1 of RT and cisplatin 60 mg/m^2 on day 1 and day 29. At a median follow-up of 5.1 years, there was no difference in complete response rate (90.5% vs. 89.6%, $p = 0.64$) and overall toxicity (71% vs. 72%) between MMC group and cisplatin group. Grade 3–4 hematologic toxicity was higher in MMC group (26% vs. 16%, $p < 0.001$) primary related to WBC toxicity; however, this did not increase the rates of febrile neutropenia (3% in both arms). Other grade 3–4 toxicities were similar between both arms (skin [48% vs. 47%], GI [16% vs. 18%]). Although the efficacy of cisplatin was similar, the ease of administration of mitomycin (a single dose of MMC given over 10 min) scores over cisplatin (two doses to be given along with hydration over a full day). This trial establishes MMC 5FU along with RT as the standard treatment in localized ACC.

RTOG 98–11 also compared cisplatin 5FU versus 5FU MMC-based chemoradiation [55]. However, the study design incorporated neoadjuvant chemotherapy in the cisplatin arm. Hence, direct comparison of RT with cisplatin or MMC is not possible. The trial showed no difference between the arms in terms of locoregional recurrence, disease-free survival or overall survival. At longer follow-up, both DFS and OS favored 5FU MMC-based chemoradiation [56].

Capecitabine is an oral prodrug of 5FU and is associated with a favorable side effect profile. Its ease of administration (lack of requirement for admission and continuous infusion) and convenience makes it a suitable alternative to 5FU. Capecitabine has safely replaced 5FU in other GI cancers. In rectal cancer, capecitabine has proven efficacy similar to 5FU in neoadjuvant setting [57]. A phase II trial of capecitabine MMC in 31 patients of ACC by Glynne-Jones et al. showed 77% complete clinical response [58]. At a short follow-up of 14 months, three locoregional relapses were seen. Capecitabine was well tolerated with minimal toxicity and good compliance. Another phase II trial by Oliviera et al. showed CR rate of 86% with a locoregional control of 86% at 24 months in 51 ACC patients [59]. Although there is lack of randomized trial proving efficacy of Capecitabine, it is already widely adopted in clinical practice with acceptable toxicity and outcomes [60–63].

Other agents have been explored to enhance the local control rates in ACC. Cetuximab has shown improved survival in Squamous Cell Carcinoma (SCC) of the head and neck and was investigated in ACC [64]. Recently, two phase trials of cetuximab (along with concurrent cisplatin and 5FU with RT) in immunocompetent as well as HIV-positive patients showed reduction of local failure with high incidence of grade 4 toxicities [65, 66]. The role of other targeted agents like Panitumumab is being tested and phase II trials are ongoing (FFCD 0904 trial and VITAL trial) [67].

6.2 Neoadjuvant and Maintenance/Consolidation Chemotherapy

Treatment intensification in ACC to improve survival was tried with neoadjuvant chemotherapy (NACT) and maintenance chemotherapy. Two large RCT trials evaluated the role of (NACT) [55, 68]. RTOG 9811 is multicentric phase III trial which compared cisplatin 5FU NACT (2 cycles) followed by cisplatin–5FU-based chemoradiation with MMC 5FU-based chemoradiation [55]. From 1998–2005, 682 ACC patients were enrolled in the trial with the primary end point being improvement in disease-free survival with NACT f/b CTRT. At a median follow-up of 2.5 years, NACT failed to improve DFS (54% vs. 60%, $p = 0.17$) or overall survival (70% vs. 75%, $p = 0.10$). The locoregional recurrence and DM rates were also similar. The colostomy rates were significantly higher in the NACT-CTRT arm (19% vs. 10%, $p = 0.02$). At a follow-up of 5 years, both DFS (67.8% vs. 57.8%, $p = 0.006$) and OS (78.3% vs. 70.7%, $p = 0.026$) were significantly higher in the CTRT alone arm [56]. Locoregional relapses were less in CTRT arm (20% vs. 27%).

UNICANCER ACCORD 03 trial is a 2 × 2 factorial trial which evaluated NACT and high-dose boost in ACC patients [69]. Two cycles of cisplatin–5FU NACT followed by cisplatin–5FU-based CTRT was compared with cisplatin–5FU-based CTRT. RT dose was 45 Gy in 25 fractions over 5 weeks in both arms. Patients were further randomized to standard boost (15 Gy) versus high-dose boost (20–25 Gy). At a median follow-up of 50 months, there was no difference in colostomy-free survival between NACT-CTRT arm and CTRT arm (76.5% vs. 75%, $p = 0.37$). Five-year OS (74.5% vs. 71%, $p = 0.81$) and local control was also similar.

ACTII trial evaluated the role of maintenance chemotherapy (two courses of Cisplatin and 5FU) after completion of chemoradiation at week 11 and 14 with the premise of reducing distant metastases and improving survival [54]. The primary end point was progression-free survival (PFS). Only 44% of patients could complete both courses of chemotherapy (64% completed at least 1 course); 33% needed dose modifications due toxicity. There was no difference in 3-year PFS between maintenance versus no maintenance group (74% vs. 73%, $p = 0.7$), irrespective of primary randomization to MMC (73% vs. 73%) versus cisplatin (74% vs. 72%). Overall, any grade 3–4 toxicity was seen in 35%; other toxicities were hematologic (7%), GI (13%) and other nonhematologic (29%). There was no benefit of maintenance chemotherapy even in the subset of advanced tumors (T3-4 and node positive). The lack of clinical benefit seen in these trials does not support neoadjuvant or maintenance chemotherapy in the management of localized SCC of anal canal.

6.3 Metastatic Disease

There is no consensus on the management of metastatic ACC, and evidence is limited to retrospective single institutional studies, case series or case reports. Cisplatin 5FU-based chemotherapy is the standard of care in metastatic/recurrent setting [70]. Faivre et al. treated 19 metastatic anal cancer patients at Gustave Roussy Institute with cisplatin–5FU chemotherapy. The regimen consisted of 5FU continuous infusion (1000 mg/m^2 for 5 days) and Cisplatin (100 mg/m^2) on day 2 repeated every 4 weeks. The median number of cycles was four. The response rate was 66% with one CR and 11 partial responses (PR). The median survival was 34.5 months with 1- and 5-year OS rates of 62.2% and 32.2%, respectively. Grade 3–4 toxicity was seen in 13%. Triplet chemotherapy (paclitaxel–carboplatin 5FU) also has been evaluated in first-line setting with 2 patients having a CR [71]. In patients relapsing after first-line chemotherapy, treatment options are limited. The evidence Paclitaxel has shown some activity in patients failing cisplatin–5FU [72]. Recently, Immunotherapy has shown encouraging results in refractory ACC patients. These initial data support further investigation of immunotherapy in ACC patients.

6.4 Chemotherapy Schedules

6.4.1 Assessment

At baseline, CBP with differential counts and platelets, renal function tests and estimated creatinine clearance and liver function test (Bilirubin, AST, Alkaline Phosphatase) are needed to be done. During treatment, CBP with differential counts and platelets and creatinine are needed to be monitored weekly. For patients on warfarin and receiving capecitabine therapy, weekly International Normalised Ratio (INR) is needed to be done until stable warfarin dose established. After treatment, counts should be monitored for 2 weeks after chemoradiation.

Concurrent chemotherapy schedule is shown in Table 2.

Table 2 The chemotherapy for concurrent administration with radiation

Drug	Dose	Administration
Mitomycin C	10 mg/m^2 on day 1 week 1 and on day 29 week 5 (week 5 mitomycin is optional) (maximum dose = 20 mg)	IV bolus.
Capecitabine	825 mg/m^2 BID daily or on days of RT. (Total daily dose = 1650 mg/m^2)	To be taken with or within 30 mins of meal. The second dose to be taken 10–12 h after first dose
5 Fluorouracil	1000 mg/m^2/day for 4 days (days 1–4 on weeks 1 & 5) (total dose = 4000 mg/m^2 over 96 h)	IV in 5% dextrose to a total volume of 192 mL by continuous infusion at 2 mL/h via appropriate infusor device

6.4.2 Toxicity

The common toxicities seen are hematologic (anemia, leucopenia, thrombocytopenia), gastrointestinal (diarrhea, stomatitis), hand foot syndrome. Myocardial ischemia or angina occurs rarely with capecitabine or 5 Fluorouracil.

7 Surgical Management

Historically, surgery was the treatment of choice for anal canal cancers. It involved an abdominoperineal resection (APR) of anal canal with permanent end colostomy. The 5-year survival with this approach was around 50–70% [73–75]. With the results of radiation ± chemotherapy, surgery is now reserved for salvage. Few indications for surgery are:

- Anal margin cancer—early stage.
- For the control of primary in locally advanced cases—Poor response or progressive local disease during/following chemoradiotherapy.
- Locally recurrent tumor—local relapse (locoregional) following chemoradiation.
- Failure of locally advanced cases—Persistent local disease or residual lymph nodes after 6 months of completion of chemoradiation.
- Persistent pain, fistula or incontinence following chemoradiation.

A temporary defunctioning colostomy may be needed prior to initiating chemoradiation in case circumferential lesion causing obstruction and involvement of rectovaginal septum

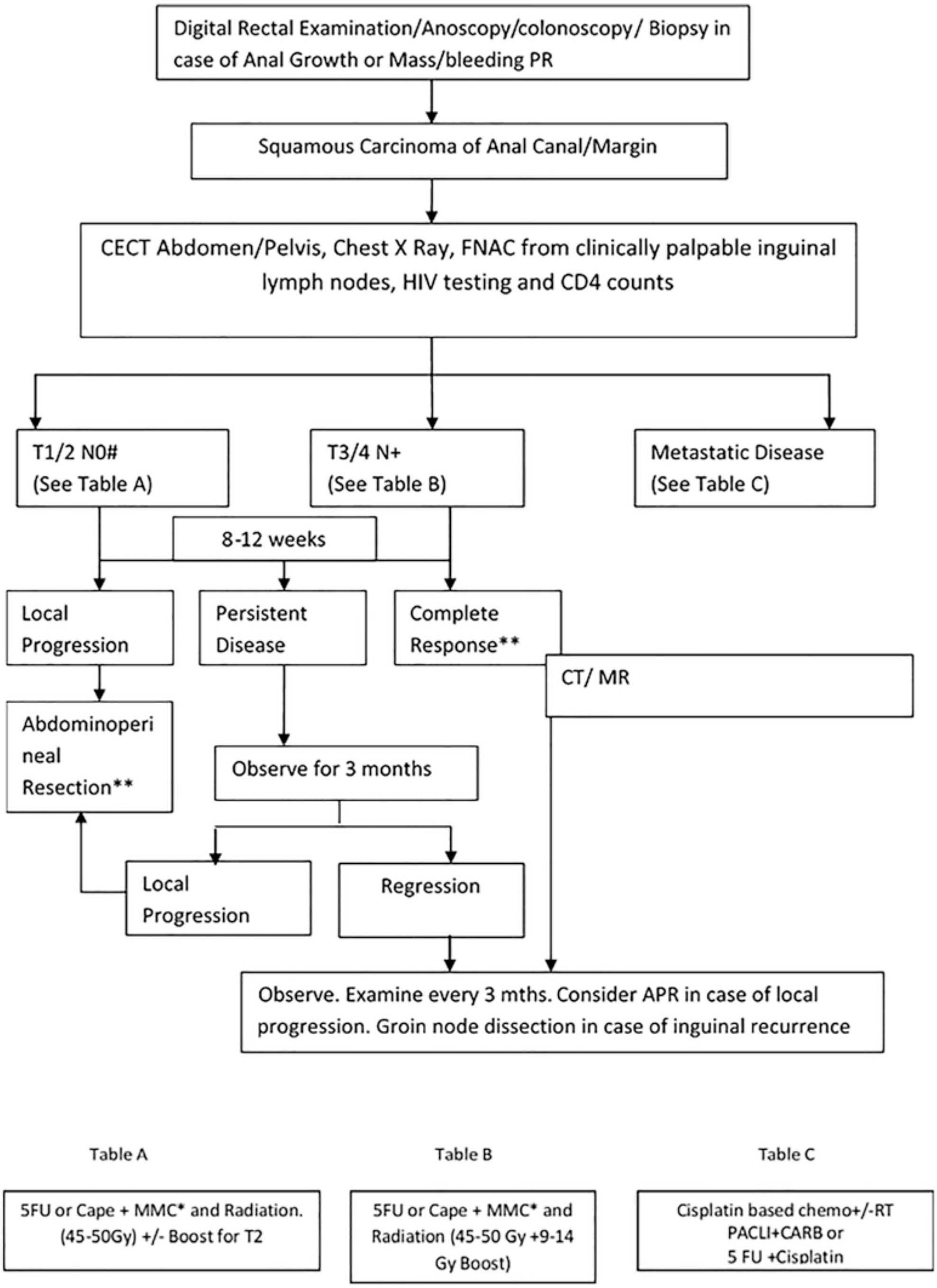
Digital Rectal Examination/Anoscopy/colonoscopy/ Biopsy in case of Anal Growth or Mass/bleeding PR
Squamous Carcinoma of Anal Canal/Margin
CECT Abdomen/Pelvis, Chest X Ray, FNAC from clinically palpable inguinal lymph nodes, HIV testing and CD4 counts
T1/2 N0# (See Table A)
T3/4 N+ (See Table B)
Metastatic Disease (See Table C)
8-12 weeks
Local Progression
Persistent Disease
Complete Response**
CT/ MR
Abdominoperineal Resection**
Observe for 3 months
Local Progression
Regression
Observe. Examine every 3 mths. Consider APR in case of local progression. Groin node dissection in case of inguinal recurrence
Table A
5FU or Cape + MMC* and Radiation. (45-50Gy) +/- Boost for T2
Table B
5FU or Cape + MMC* and Radiation (45-50 Gy +9-14 Gy Boost)
Table C
Cisplatin based chemo+/-RT PACLI+CARB or 5 FU +Cisplatin

Fig. 1 Stage-wise management algorithm for anal canal cancer

Table 3 The stage-wise prognosis for anal canal cancer

Stage	OS (%)
I	86
IIA	86
IIB	76
IIIA	60
IIIB	54
IIIC	45
IV	20

with fistula. Colostomy reversal may be done after 6 months of completion of chemoradiation if locoregionally controlled.

8 Stage-Wise Management Algorithms (Fig. 1)

9 Stage-Wise Prognosis with Current RX (Table 3)

10 Management of Recurrent Disease Including Specific Palliative Measures

Majority of recurrences occur within 2 years of completion of treatment (about 50%) either in primary or in the pelvic/inguinal nodes [76]. Local recurrence or persistence of local disease is an incurable condition and severely affects the quality of life of patients. Patients may present with severe pelvic pain, obstruction, bleeding local infection and incontinence as tumor invades the surrounding tissues. A complete restaging with either PET-CT or CECT thorax, abdomen and pelvis is to be done. If localized disease, salvage APR needs to be considered [77]. If there is extensive local disease and R0 resection is not feasible, a defunctioning colostomy followed by either palliative reirradiation or chemotherapy may be considered.

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Gastroenteropancreatic Neuroendocrine Tumors

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Abbreviations

ACTH	Adrenocorticotropic hormone
CRH	Corticotrophin releasing hormone
CT	Computed tomography
EUS	Endoscopic ultrasound
F-NET	Functional NET
GEP-NET	Gastroentero-pancreatic neuroendocrine tumor
IHC	Immunohistochemistry
LAR	Long-acting repeatable
MEN-1	Multiple endocrine neoplasia type 1
MRI	Magnetic resonance imaging
NEC	Neuroendocrine carcinoma
NET	Neuroendocrine tumor
NF-NET	Non-functional NET
NSE	Neuron-specific enolase
PP	Pancreatic polypeptide
PPI	Proton pump inhibitors
PRRT	Peptide receptor radionuclide therapy
SEER	Surveillance, Epidemiology, and End Results
SSA	Somatostatin analogs
TACE	Transarterial chemo-embolization
TARE	Transarterial radio embolization
TS	Tuberous sclerosis
VHL	Von Hippel Lindau syndrome
VIP	Vasoactive intestinal polypeptide

1 Introduction

Gastroentero-pancreatic neuroendocrine tumors (GEP-NETs) is a heterogeneous group of tumors originating from enterochromaffin cells (neuroendocrine) of the gut and are commonly located in the stomach, colorectum, small intestine, and pancreas. In the past, these tumors were described by various terms like APUDomas, Kulchitsky cell tumors, Argentafinomas, carcinoid tumors, and pancreatic islet tumors, accounting for the heterogeneous information and data in the literature [1]. In 2000, World Health Organisation (WHO) developed a universal nomenclature and classification system and termed them as neuroendocrine tumors (NETs). NETs arising from the gastrointestinal tract and pancreas are collectively referred to as GEP-NETs as they share similar treatment principles and guidelines.

2 Epidemiology

The annual incidence and prevalence rate of NETs is rising steadily around the world in recent years, as compared to other malignancies. According to the Surveillance, Epidemiology and End Results (SEER) database, the age-adjusted incidence of NETs has increased from 1.09 cases per 100,000 population in the year 1973 to 6.98 cases per 100,000 population in year 2012. GEP-NETs are more prevalent than most of the epithelial gastro-intestinal cancers except colorectal cancer [2]. This increase in incidence may be probably due to the ready availability of diagnostic modalities, widespread use of imaging, and increased information amongst physicians. GEP-NETs are the most commonly encountered NETs, accounting for 58% of all the NETs. GEP-NETs can occur at all ages but are usually diagnosed after the fifth decade of life and exhibit slight male preponderance. The small intestine is the most commonest GEP-NET site followed by the pancreas, stomach, colon, and rectum. Significant geographical

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variation in site predilection is noted and NETs at these sites differ clinico-epidemiologically. GEPNETs usually occur sporadically but 5–25% of cases are associated with some familial or genetic predisposition. Familial syndromes associated with GEP-NETs (particularly pancreatic NETs) are multiple endocrine neoplasia type 1 (MEN-1), von Hippel Lindau syndrome (VHL), von Recklinghausen syndrome (NF-1) and tuberous sclerosis (TS). 53% of patients with NETs present with localized disease, 20% have loco-regional disease, and 27% have distant metastases at the time of diagnosis and there are no identified environmental risk factors [2–7].

3 Pathology, Who Classification and Staging

Multipotent stem cells give rise to all epithelial cells (including neuroendocrine) in the pancreas and gastrointestinal tract. These cells produce a variety of hormones like vasoactive intestinal polypeptide (VIP), gastrin, glucagon, insulin, ghrelin, pancreatic polypeptide (PP), somatostatin, corticotrophin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). NETs producing one of these hormones/peptides are referred to as functional NETs (F-NET), while those without any hormone production are termed non-functional NETs (NF-NET).

Neuroendocrine markers like chromogranin A, synaptophysin, neuron-specific enolase (NSE), and CD 56 are expressed by GEPNETs. A thorough description of the macroscopic, microscopic, and immunohistochemical findings is important to support the diagnosis of NETs and to allow a correct classification, staging, and grading. Specific staining for hormones can also be used to confirm the source of clinical symptoms, but the immunohistochemical demonstration of a hormone alone is not proof of the functionality of a NET. The biological behavior of GEP-NETs is dependent on the degree of differentiation and rate of proliferation. Degree of differentiation is the extent to which tumor cells resemble normal cells and the rate of proliferation is defined by the number of mitoses per 10 high-power microscopic fields (mitotic rate), or as the percentage of tumor cells exhibiting immune-positivity Ki-67 antigen (Ki-67 index). Well-differentiated NETs are usually of low or intermediate grade; poorly differentiated NETs are usually high grades (Fig. 1) [8–10]. Immunohistochemistry for Ki-67 (MIB-1) is a must to grade the tumor according to the new World Health Organization (WHO) classification. This classification is applicable to NETs of all sites and has been revised in 2017 (Table 1) [11].

G3 NEC tumors with Ki 67 index <55% are less responsive to platinum-based chemotherapy but still have a good prognosis and survival than chemo-responsive tumors with an index >55% [12]. NETs with lower proliferative index behave more like G2 NETs than aggressive G3 neuroendocrine carcinoma (NEC). New WHO classification proposes G3 NET as a separate group of tumors that behave more like NETs than NECs. These tumors often evolve from a lower grade, usually have Ki 67 index between 20–50%, and mitotic counts less than 20/10 HPF. G3 NETs predominantly show MEN1, DAX, and ATRX mutations, whereas G3 NECs are poorly differentiated with P53 and RB1 mutations and the ki67 index usually is >50%. The most commonly used staging system for GEP-NETs is AJCC -TNM staging system, which has been revised recently. In contrast to the previous edition, NETs are included in the respective organ chapters [13].

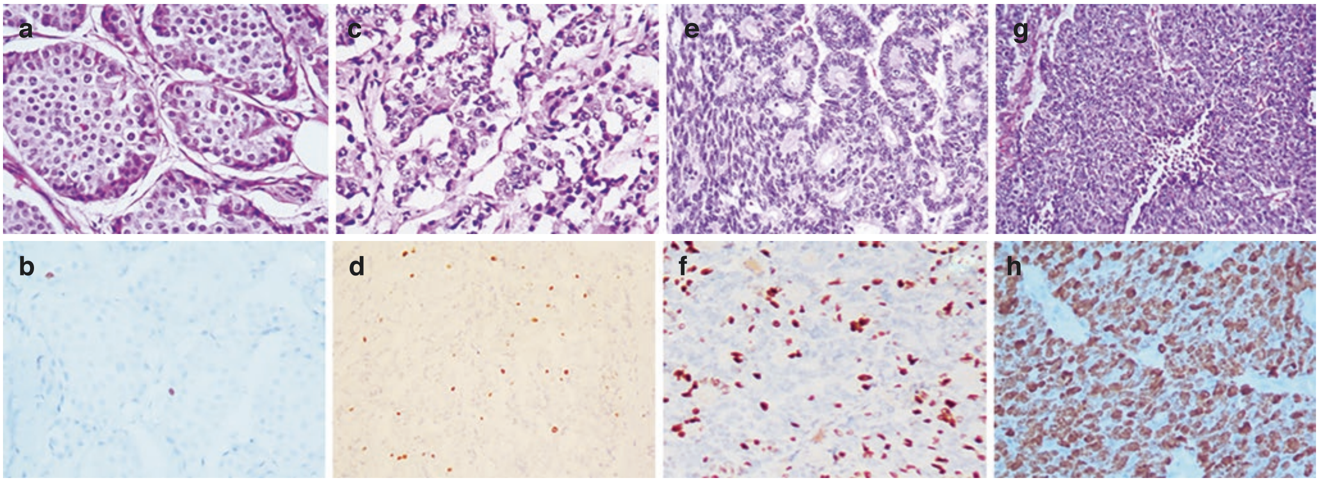


Fig. 1 Microscopic appearance of neuroendocrine tumors. (**a, b**) Grade 1 neuroendocrine tumor with Ki-67 index of 1%. (**c, d**) Grade 2 neuroendocrine tumor with Ki-67 index of 7%. (**e, f**) Grade 3 neuroendocrine tumor with a Ki-67 index of 37%. (**g, h**) Grade 3 neuroendocrine carcinoma with a Ki-67 index of 95%. (**a, c, e, g**) H & E stain. (**b, d, f, g**) Immunostain. Images courtesy of Professor Munita Bal, Department of Pathology, Tata Memorial Hospital, Mumbai

Table 1 World Health Organization 2017 classification of the NETs[a]

Grade	Mitotic count (hpf)	Ki-67 index	Morphology
G1 NET	<2/10	<3	Well-differentiated
G2 NET	2–20/10	3–20	Well-differentiated
G3 NET	>20/10	>20	Well-differentiated
G3 NEC	>20/10	>20	Poorly differentiated (small/large cell)
[b]*Mixed endocrine non-endocrine neoplasm (MiNEN):* NETs with a component of a non-endocrine carcinoma (squamous, adenocarcinoma, or acinar cell carcinoma) combined with a neuroendocrine neoplasm. Usually, both components are high grade (G3), but occasionally one of the two or both components may belong to the G1/G2 category. To qualify for a MiNEN, each component should comprise at least 30% of the tumor cell population.			

NET neuroendocrine tumor

[a] This classification was devised primarily for pancreatic NETs. Used with permission from Lloyd RV, Osamura RY, Kloppel G, Rosai J. WHO Classification of Tumours of Endocrine Organs. Lyon, France: IARC; 2017

[b] Features of MiNEN are not detailed in WHO 2017 classification

Poorly differentiated NECs should be staged as per TNM staging for the adenocarcinoma of the respective organ. Further details of AJCC staging can be accessed at https://www.annalsofoncology.org/cms/10.1016/j.annonc.2020.03.304/attachment/05ebe256-f288-45b8-b76d-6fa4403926b3/mmc1.pdf [page 11]).

4 Evaluation and Work-Up

All the cases of suspected GEP-NETs should be evaluated in a stepwise manner to avoid unnecessary investigations and to fast-track the evaluation process.

4.1 Tumor Markers

General/non-specific markers (chromogranin A, Cg A/neuron-specific enolase, NSE) can be elevated in both F-NETs/NF-NETs, whereas specific markers (gastrin, pancreatic polypeptide, insulin) are elevated in F-NETs.

4.1.1 Serum Chromogranin a (cg a)

Serum chromogranin A (Cg A), a glycoprotein marker, secreted by neuroendocrine cells, is raised in both F-NET and NF-NETs. It serves as a predictor of disease burden, response evaluation, and prognostic factors. False positive raised Cg A levels are seen with chronic PPI use, atrophic gastritis, inflammatory bowel disease, renal failure, liver cirrhosis, and malignancies like hepatocellular carcinoma and pancreatic cancer. In patients with poorly differentiated G3 tumors, Cg A is often normal, but serum neuron-specific enolase (NSE) can sometimes be of value as a general marker [14, 15].

4.2 Radiological Imaging

4.2.1 Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) [16, 17]

Cross-sectional imaging in the form of a contrast-enhanced CT scan is the most commonly used and mandatory imaging tool for the localization and characterization of NETs. NETs have rich arterial supply and enhance very well in the early arterial phase (Fig. 2). MRI is occasionally used as an adjunct to CT imaging, they exhibit low signal intensity on T1-weighted sequences and high signal intensity on T2-weighted sequences. NETs are more prominent on fat-suppressed T1-weighted sequences showing low signal intensity as compared to the pancreas. Sensitivities of various imaging modalities are depicted in Table 2.

4.2.2 Endoscopic Ultrasound (EUS) [18]

EUS can detect and localize the lesions as small as 2–3 mm that are missed on CECT and are particularly useful for gastric and pancreatic NETs. It can also be used for obtaining cytology and biopsy to establish tissue diagnosis. However, this is an operator-dependent test requiring skills and expertise.

4.2.3 ^{68}Ga DOTATATE PET CT and ^{18}FDG PET CT Scan [19–24]

Somatostatin, a peptide produced by endocrine cells in the gastrointestinal tract requires attachment to SSTRs, which are coupled to cell membrane G-proteins. Over-expression of SSTRs in NETs forms the basis of SSTR-based radionuclide imaging, where a radiolabeled ligand is used to bind to SSTR. Five SSTR subtypes are known, of which SSTR2 and SSTR5 are abundant, with SSTR2 being particularly useful for clinical practice. PET-CT scan with somatostatin analogs like ^{68}Ga-DOTATATE and ^{18}FDG is the most commonly performed functional imaging in the current era. Potential benefits of these analogs include lower radiation dose, potentially greater diagnostic accuracy, and greater patient convenience. With increasing proliferation (as measured by Mib index or Ki-67), SSTR expression decreases and tumors may not have uptake on SSTR imaging. In such situations, an 18F-FDG PET CT scan can be used. An increased 18-FDG uptake correlates with loss of differentiation, higher grade, and adverse

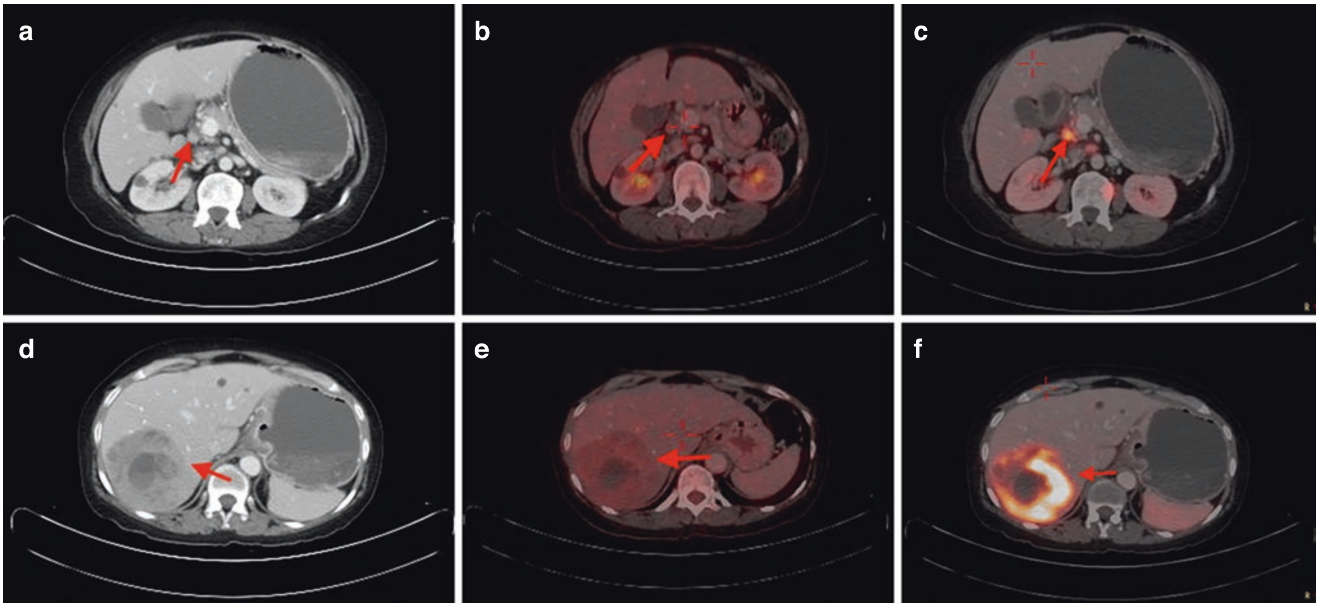


Fig. 2 Radiological appearance of neuroendocrine tumors, small primary lesion at the junction of the first and second parts of the duodenum with a large metastatic lesion in the liver. (**a, d**) Contrast-enhanced CT, heterogeneous enhancement. (**b, e**) FDG PET, low-grade uptake, SUVmax-6.3. (**c, f**) FDG PET, intense tracer uptake, SUVmax-93.44

Table 2 Sensitivity and specificities of different imaging modalities

Imaging	Sensitivity (%)	Specificity (%)
USG	13–27	–
CECT	57–94	83–100
MRI	77–94	78–100
EUS	82–93	87–98
^{68}Ga DOTATOC PET	87–96	88–95

USG ultrasonography, *CECT* contrast-enhanced computed tomography, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasonography, ^{68}*Ga DOTATOC PET* DOTA positron emission tomography

biologic behavior of the tumor. There is increasing use of dual PET imaging in the current era, especially with higher grade NETs and progressive disease therapy. Besides an improved sensitivity when using hybrid imaging (FDG and DOTA PET), this kind of imaging can also be used for response assessment after peptide receptor radionuclide therapy (PRRT) to evaluate for tumor dedifferentiation or the "flip-flop" phenomenon (high DOTATATE and low FDG uptake in well-differentiated tumors and the opposite imaging phenotype in poorly differentiated tumors). However, the high costs involved limit its availability and use to few centers. SSTR-based imaging for the diagnosis of insulinoma has a lower sensitivity (25–60%), as compared to that for other NETs. The role of various imaging modalities in the evaluation and management of GEP-NETs is elaborated in Table 3.

Table 3 Role of various investigations/imaging modalities in the evaluation and management of GEP-NETs

NET Site	Localization	Staging	Treatment selection
Gastric	CECT, EUS, SRI	CECT+SRI	Endoscopy-resection SRI-SA, PRRT
Duodenum	SRI, EUS	CECT+SRI	SRI: SA, PRRT CECT/MRI: Surgery
Small intestine	SRI, capsule endoscopy, CECT	SRI + CECT/MRI	SRI: SSA, PRRT CECT/MRI: Surgery
Colorectal	Endoscopy, EUS, SRI, CECT	SRI + CECT/MRI	Endoscopy: Resection SRI: SA, PRRT CECT: Surgery
Pancreas	SRI, EUS, CECT/MRI	SRI + CECT/MRI	SRI: SA, PRRT CECT/MRI: Surgery

GEPNETs gastroentero-pancreatic neuroendocrine tumors, *CECT* contrast-enhanced computed tomography, *SRI* somatostatin receptor imaging, *EUS* endoscopic ultrasonography, *SA* somatostatin analogs, *PRRT* peptide receptor radionucleotide therapy

4.3 Immunohistochemistry (IHC) [25, 26]

Immunohistochemical staining on biopsy specimens is a must to establish the tissue diagnosis of NETs. While chromogranin A and synaptophysin are the two main and most commonly used IHC markers, CD56, neuron-specific enolase (NSE), and cytokeratin are also important markers, especially in equivocal cases. F-NETs also show expression of peptides such as insulin, gastrin, glucagon, VIP, and somatostatin. Chromogranin A is a specific marker of neuroendocrine differentiation and its positivity is reduced with increasing grade of the tumors. Poorly differentiated NECs may not express chromogranin and may express synaptophysin only. Synaptophysin is a highly sensitive marker but lacks specificity and can be positive in other tumors like acinar cell carcinoma or pseudopapillary tumors. Focal positivity of synaptophysin in the absence of chromogranin A positivity should raise suspicion of pathologies other than NET and the use of additional markers may be necessary.

5 Clinical Presentation

GEP-NETs are a heterogeneous group of tumors, each with specific characteristics and biological behavior. Individual discussion of each entity is beyond the scope of this chapter, however, relevant salient features are elaborated in Table 4 [27–37]. The general outline for the evaluation and management remains the same and is more emphasized here. NF-NETs are more prevalent than F-NETs and the radiological appearance of a hyper-vascular tumor with signs/symptoms pertaining to the specific site remains the most common mode of presentation for these tumors. NF-NETs have poor outcomes as compared to F-NETs, likely due to late presentation.

Table 4 Salient features of gastroentero-pancreatic neuroendocrine tumors

NET	Location	Salient features	Clinical features	Diagnosis	Treatment	5-year survival
Insulinoma	• Equally distributed throughout the pancreas	• MC PNET • ≈ 90% solitary • ≈ 90% benign • ≈ 90% sporadic • ≈ 90% amenable to surgical resection • ≈ 90% are <2 cm. • ≈ 5–10% are associated with MEN 1 syndrome (often multiple)	• Fifth decade of life • females>males • Recurrent attacks of hypoglycemia with blood sugar <50 mg/dL and relief from symptoms of ingestion of glucose. • Neurological symptoms—confusion, visual disturbances, amnesia, altered consciousness • Vasomotor symptoms- sweating, weakness, palpitations, tremor, paresthesias, and hunger.	• 72-h fasting test-gold standard • Whipples triad • Blood glucose levels below 50 mg/dL • insulin levels equal to or greater than 6 mU/mL • Elevated C-peptide levels (> = 200 pmol/L). • Absence of sulfonylurea in the plasma • Arterial stimulation and venous sampling- historical in the current era. • Cross-sectional imaging- CECT • Functional imaging- ^{68}Ga DOTATATE PET/^{18}FDG PET scan	• Surgery • Usually enucleation/ pancreas preserving resection • Percutaneous ablation in unwilling/unfit patients	• 80–95%
Gastrinoma	80% in Gastrinoma triangle (Passaro's)- confluence of cystic and common bile duct superiorly, the junction of second and third parts of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially.	• Second MC PNET • 60% malignant • 50% multifocal • Multifocal tumors in MEN 1 syndrome	• Fifth to sixth decade • Abdominal pain, heartburn, diarrhea • Zollinger Ellison syndrome- pancreatic tumor, symptomatic acid hyper-secretion, and peptic ulceration.	• Serum gastrin levels >1000 pg/mL with gastric pH <2 • Secretin stimulation test • Basal acid output of >15 mEq/h • Cross-sectional/ functional imaging (see above)	• Solitary lesions- surgery with lymphadenectomy. • Multifocal lesions- enucleation of lesions more than 2 cm. • Intractable symptoms/ metastatic disease- PPI/ octreotide/PRRT.	• 50–70%
Glucaganoma	Body and tail	• Rare • 60–70% malignant	• Fifth decade • Equal gender distribution • 4 ds—Diabetes, dermatitis, deep vein thrombosis, depression. • Necrolytic migratory erythema	• Serum glucagon level > 1000 pg/mL • cross-sectional/ functional imaging (see above)	• Resectable- surgery- primary and metastatic sites. • Unresectable- somatostatin analogs for symptom control. • Chemotherapy- dacarbazine, streptozocin.	• 50–60%.

Somatostatinoma	Pancreas, duodenum, and sometimes biliary tract	• 1% of pancreatic NETs • 90% solitary	• Fifth decade • equal gender distribution • Somatostatinoma syndrome-hyperglycaemia, Cholelithiasis, steatorrhea, and diarrhea. • Pain, obstructive jaundice, gastric outlet obstruction, bleeding	• Serum somatostatin level > 160 pg/mL • Cross-sectional/functional imaging (see above)	• Surgery/debulking • Somatostatin analogs	• 20–40%
VIPoma	• Body and tail	• Usually benign • Verner Morrison/WDHA syndrome-watery diarrhea, hypokalemia, achlorhydria	• Fifth decade • Flushing • Weight loss • Secretary diarrhea-painless, odorless, 6–8 L/day	• Serum VIP level > 200 pg/mL • Cross sectional/functional imaging (see above)	• Symptom control-somatostatin analogs, glucocorticoids • Surgery/debulking • Chemotherapy-streptozocin	• 40–50%
Small intestinal NET	• ileum > jejunum >duodenum	• Most common (30–50%) small bowel neoplasm. • 25% are multifocal • 20–30% have carcinoid syndrome • Highest risk of distant metastasis amongst NETs. • Malignant potential is directly correlated with size.	• 6–seventh decade • male>female • Abdominal pain, diarrhea, bleeding • Carcinoid syndrome-episodic flushing, wheezing, palpitations, diarrhea	• Serum chromogranin A and urinary 5-HIAA • Cross-sectional/functional imaging-see above	• Surgery-resection with regional lymphadenectomy • PRRT • Somatostatin analogs	• Localized- 65% • Loco-regional–71% • Metastatic-54%

(continued)

Table 4 (continued)

NET	Location	Salient features	Clinical features	Diagnosis	Treatment	5-year survival
Gastric NET	• Antrum> body>fundus.	• Most common form of GEP-NETs. • 3 types • Type I: MC, associated with chronic atrophic gastritis, hypergastrinemia, and multifocal, polypoidal tumors. • Type II: Associated with hypergastrinemia, underlying Gastrinoma, MEN 1, and small multifocal tumors. • Type III: Sporadic, often large, not associated with hypergastrinemia, and have high malignant/ metastatic potential.	Type I: 6-seventh decade, female>male, s/s of chronic atrophic gastritis, pernicious anemia. Type II: Fifth decade, s/s of Zollinger Ellison syndrome Type III: Sixth decade, males> females, pain	• endoscopy • Type I: High serum gastrin, chronic atrophic gastritis on biopsy, and high gastric pH. • Type II: High serum gastrin and low gastric pH. • Type III: Mass lesion on endoscopy and imaging.	Type I: • <2 cm-Netazepide, endoscopic polypectomy. • >2 cm, >6 lesions, recurrent- surgery. Type II: Treatment of Gastrinoma. • <2 cm-endoscopic resection. • >2 cm, >6 lesions, recurrent- surgery. Type III: Surgical resection with lymphadenectomy.	• Localized- 73% • Loco-regional–65% • Metastatic-25%
Appendiceal NET	• tip of the appendix	• 1 in 300 appendectomies • Usually incidental diagnosis • Malignant potential directly proportional to the size of the tumor	• Fourth decade • females>males • Acute/subacute appendicitis	• Cross-sectional/ functional imaging- see above	• Tumors <2 cm: Appendicectomy • Tumors >2 cm, positive margins or mesoappendiceal involvement: Right hemicolectomy	• Localized- 88% • Loco-regional–78% • Metastatic-25%
Colorectal NET	• rectum> colon • usually mid rectum. • right colon> left colon	• Colonic tumors are more aggressive than rectal tumors. • Malignant potential directly proportional to the size of the tumor	• Males> females • Fifth decade • Rectal bleeding, pain, change in bowel habits	• Endoscopy • Cross-sectional/ functional imaging (see above)	• Endoscopic removal • Transanal endoscopic microsurgery Surgical resection	Colon- • Localized- 85% • Loco-regional–46% Metastatic-14% Rectum- • Localized- 90% • Loco-regional–62% • Metastatic-24%

6 Carcinoid Syndrome and Carcinoid Heart Disease [38–40]

This syndrome is characterized by diarrhea, flushing, and bronchospasm. It is usually seen with small intestinal NETs with liver metastasis. Peptides, particularly serotonin, and prostaglandins secreted by liver metastasis are responsible for the clinical manifestations as these mediators are directly secreted in systemic circulation and spared of metabolism in the liver. Flushing typically involves the face, neck, and upper body and may be precipitated by alcohol, stress, spices, and tyramine-containing foods. Carcinoid heart disease is typically seen in patients with high levels of serum serotonin, causing fibrosis of the right-sided cardiac valves, leading to tricuspid regurgitation and pulmonary valve stenosis. The incidence of carcinoid heart disease is declining, as a consequence of the use of serotonin-inhibiting therapies. Transthoracic echocardiography should be performed annually in patients with carcinoid heart disease; cardiac MRI is helpful in assessing the severity of endocardial fibrosis. Patients with carcinoid syndrome undergoing surgery sometimes develop a circulatory collapse due to the acute release of serotonin and other peptides leading to a carcinoid crisis. Carcinoid crisis is triggered by general anesthesia, epinephrine, handling of tumors, and hence prophylactic octreotide 250–500 μg subcutaneously, 1–2 h before surgery is recommended to avoid the crisis.

7 Principles of Management

Selecting the right modality in the right sequence is crucial for better outcomes in GEP-NETs. It is strongly recommended that such cases are managed in a high-volume center with enough experience and interest in dealing with GEP-NETs. Various modalities available for NETs in the armamentarium of oncologists are surgery, somatostatin analogs (SSA), cytotoxic chemotherapy, targeted therapy, and peptide receptor radionuclide therapy (PRRT). As the literature information is heterogeneous on GEP-NETs, the decision on offering the right treatment in a sequential manner is crucial. The treatment algorithm, followed at Tata Memorial Centre for GEP-NETs is depicted in Figs. 3 and 4. Treatment of functional GEP-NETs differs that from of non-functional GEP-NETs and symptom control takes priority in the former (see Table 4 for details).

Steps in the management of these tumors are as follows:

- Establish the preliminary diagnosis based on clinico-radiological findings.
- Confirm the tissue diagnosis with biopsy and immunohistochemistry.
- Know the functional status- based on symptoms and then specific hormone level estimation (see Table 4).
- Finally, depending on the site, grade, symptoms, and tumor burden appropriate treatment is decided. It is strongly recommended to discuss and plan the treatment in the multidis-

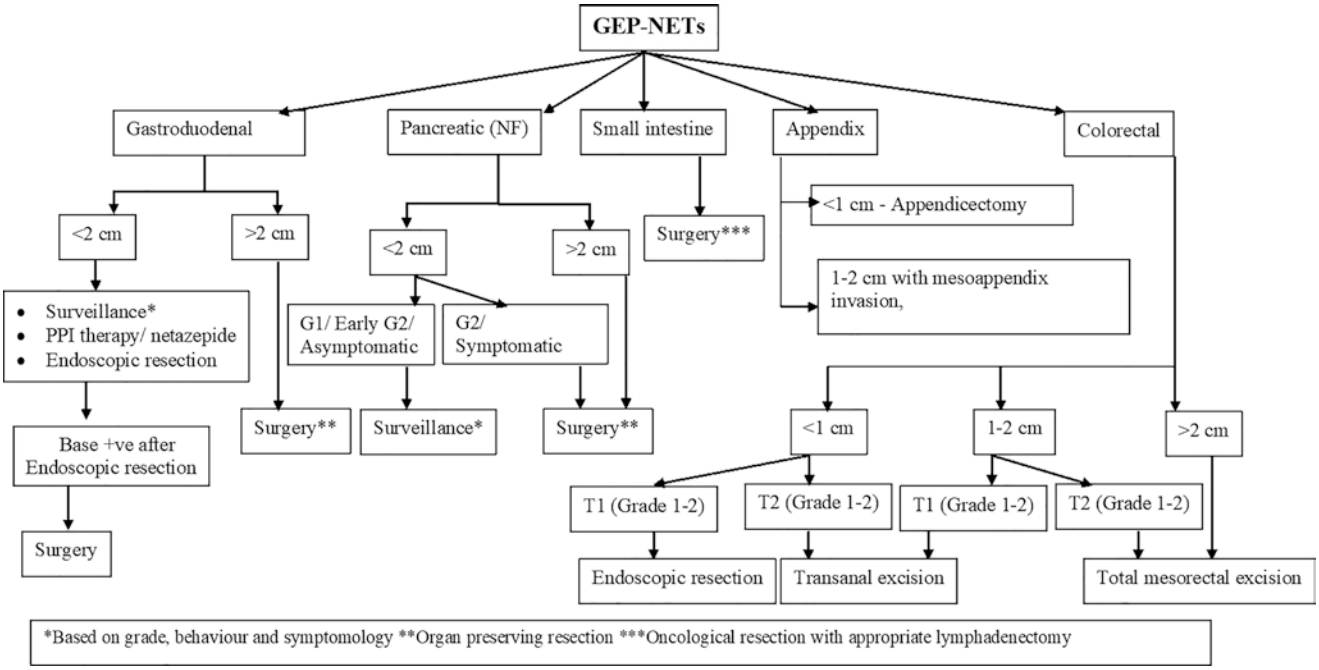
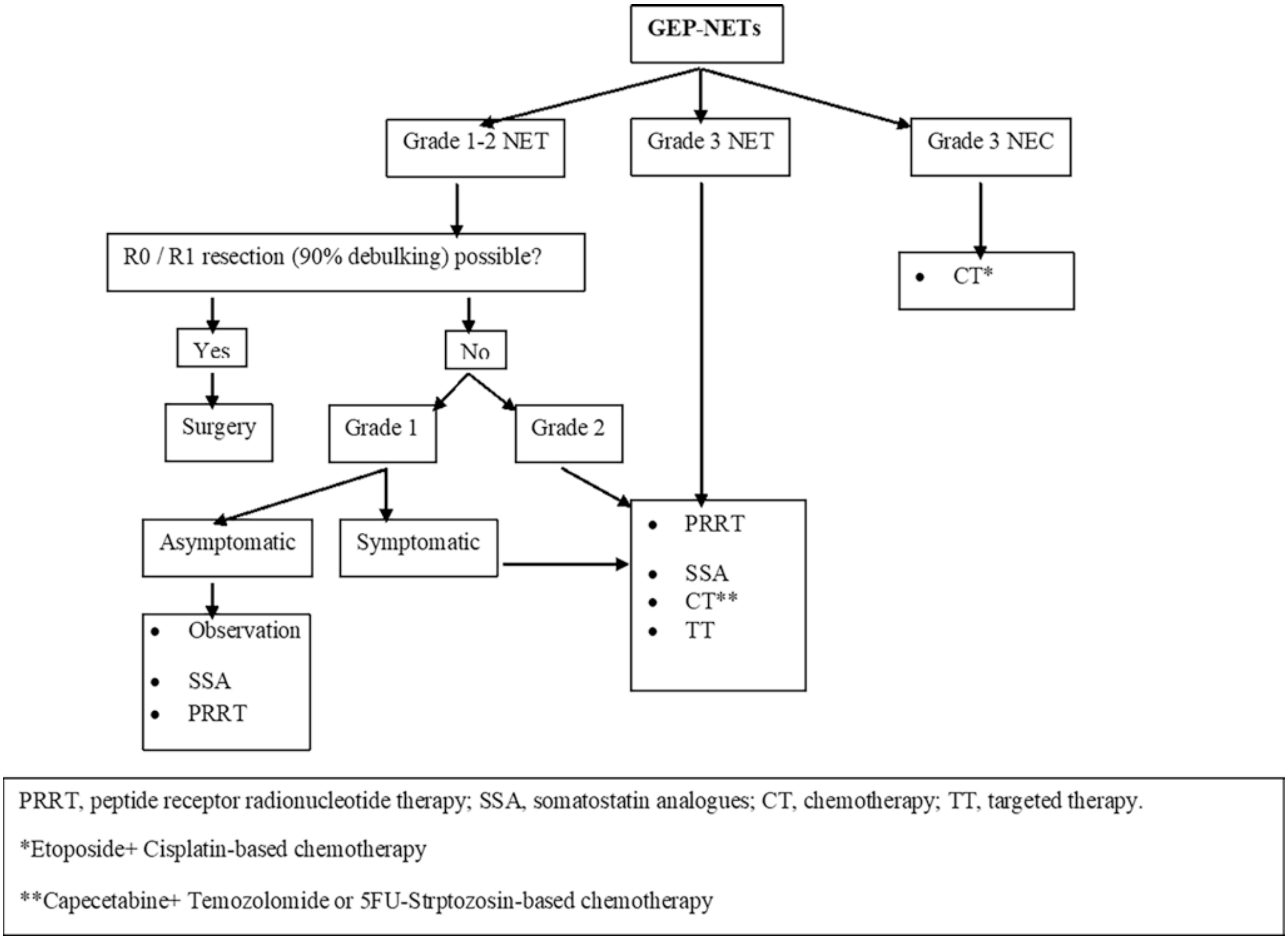

GEP-NETs
Gastroduodenal
Pancreatic (NF)
Small intestine
Appendix
Colorectal
<2 cm
>2 cm
Surveillance*
PPI therapy/ netazepide
Endoscopic resection
Base +ve after Endoscopic resection
Surgery
Surgery**
<2 cm
>2 cm
G1/ Early G2/ Asymptomatic
G2/ Symptomatic
Surveillance*
Surgery**
Surgery***
<1 cm - Appendicectomy
1-2 cm with mesoappendix invasion,
<1 cm
1-2 cm
>2 cm
T1 (Grade 1-2)
T2 (Grade 1-2)
T1 (Grade 1-2)
T2 (Grade 1-2)
Endoscopic resection
Transanal excision
Total mesorectal excision
*Based on grade, behaviour and symptomology **Organ preserving resection ***Oncological resection with appropriate lymphadenectomy

Fig. 3 Practical algorithm for the management of localized/loco-regional GEP-NETs



PRRT, peptide receptor radionucleotide therapy; SSA, somatostatin analogues; CT, chemotherapy; TT, targeted therapy.

*Etoposide+ Cisplatin-based chemotherapy

**Capecetabine+ Temozolomide or 5FU-Strptozosin-based chemotherapy

Fig. 4 Practical algorithm for the management of advanced/metastatic/recurrent GEP-NETs

ciplinary meeting. Treatment often involves the integration of multiple treatment modalities like surgery, radionuclide therapy, somatostatin analogs, and chemotherapy.

8 Treatment of Localized/Loco-Regional Tumors [35, 41–45]

Surgery is the mainstay of treatment for localized or loco-regional GEP-NETs. Table 4 depicts the various treatment options for GEP-NETS. The type and extent of surgery depends on the organ involved and disease burden. In general, oncological resection with regional lymphadenectomy is recommended. Small and lower-grade gastroduodenal and rectal NETs can be treated with endoscopic resection followed by regular surveillance. Incomplete endoscopic resection or recurrence following such conservative treatment should be treated with more radical oncological resection. NF-PNET patients with symptomatic, intermediate-to-high grade, or > 2 cm requires formal oncologic surgery. Small, localized PNETs can be managed with enucleation, however, this approach lacks oncologic adequacy in terms of lymphadenectomy and resection margins. Incidentally detected low-grade NF-PNETs, <2 cm in size can be kept under close surveillance.

The choice of surgery in small intestinal NETs primarily depends on tumor location. Jejunal and proximal ileal tumors should be treated with segmental resection and regional lymphadenectomy, whereas tumors in the distal ileum, may require formal right hemicolectomy. Around 25% of small intestinal NETs are multifocal, demanding a thorough inspection and palpation of the entire small bowel intraoperatively. Appendiceal NETs <1 cm are managed with appendicectomy alone, completion with right hemicolectomy is recommended for tumors >2 cm. Rectal NETs can be treated with endoscopic resection, transanal excision, or total mesorectal excision depending on the size of the tumor. Low anterior resection or abdominoperineal resection with lymph node sampling should be performed for larger rectal tumors.

9 Treatment of Advanced/Metastatic/Recurrent Tumors

The current era has witnessed remarkable improvements and development in treatment modalities of metastatic GEP-NETs. Systemic therapy remains the cornerstone in the management of advanced/metastatic/recurrent NETs. Various options for systemic therapy are somatostatin analogs, peptide receptor radionuclide therapy (PRRT), interferon, everolimus, sunitinib, bevacizumab, and cytotoxic regimens. The choice of systemic therapy depends on the primary site, grade, Ki 67 index, SSTR expression, disease burden, functional status, and symptoms. The main objectives of treatment in advanced cases are symptom control and prolongation of survival. Octreotide (long-acting repeatable, LAR), a somatostatin analog is the most commonly used drug for symptom control especially in carcinoid syndrome. Similarly, high-dose proton pump inhibitors (PPI) are used in gastrinoma [46]. Although surgery is not curative in metastatic settings, it still has a definite value in certain clinical situations like small intestinal NETs with obstructive symptoms, mesenteric NETs in close proximity of major vessels, and limited metastatic disease where complete resection of primary and metastatic disease is feasible. Surgery may also be indicated for palliative debulking to decrease tumor burden or to control hormone production. Liver-directed therapies like transarterial embolization, transarterial chemoembolization, and transarterial radio embolization are also options in symptomatic patients with liver-dominant metastatic disease [47–51]. Various studies pertaining to the evaluation of these modalities are summarised in Table 5. It is strongly recommended that all the cases of advanced NETs are discussed in multidisciplinary group meetings for deciding the treatment modality.

9.1 Somatostatin Analogues (SSA)

Octreotide and lanreotide are the commonly used SSAs in GEP-NETs and current evidence suggests that, in addition to symptom control, octreotide also has antiproliferative, and potentially, anticancer effects [52]. PROMID study compared octreotide LAR with placebo in midgut NETs and observed statistically significant improvement in median progression-free survival with octreotide LAR (14.3 vs. 6 months; $p < 0.001$) [53]. CLARINET study, compared lanreotide with placebo and observed significant improvement in progression-free survival (median not reached vs. median of 18.0 months, $p < 0.001$) [54]. These two studies established the role of SSA as the initial line of therapy in advanced NETs for symptomatic relief as well as prolongation of survival. Interestingly, both functional and non-functional NETs derive survival benefits from SSA. A combination of Interferon-alfa and SSA has also been studied, but these studies did not show any benefit of adding interferon to octreotide [55–57]. Currently, there is no evidence to suggest the superiority of octreotide over lanreotide and vice versa, also it is not clear whether treatment with SSAs is better than "watch-and-wait" approach in patients with the very slow-growing disease.

9.2 Chemotherapy

Cytotoxic chemotherapy with cisplatin + etoposide is the primary modality of treatment for patients with grade III neuroendocrine carcinoma. The objective response rate following this combination chemotherapy is around 42–67% with the rapid response but remissions are of short duration. Fit patients progressing on first-line chemotherapy may be offered second-line chemotherapy with FOLFIRI or FOLFIRINOX with varying response rates [12, 58–62]. Grade I-III GEP-NETs not responding or progressing on other modalities can be treated with cytotoxic chemotherapy with streptozocin, 5-FU, temozolomide, or capecitabine. Streptozocin-based combinations regimens have shown response rates in the range of 35–69%. Kunz et al. studied the role of capecitabine + temozolomide versus temozolomide alone in 144, G1/G2 NET patients and found significantly improved progression-free survival with capecitabine + temozolomide (22.7 months vs. 14.4 months, p-0.023) [63–66].

Table 5 Studies evaluating systemic therapies in GEP-NETs

Study	Reference no.	Year	No of participants	Study arms	PFS (months)	*p*-value
Rinke et al. (PROMID)	53	2009	84	Placebo vs. octreotide	6 vs. 14.3	<0.001
Raymond et al.	71	2011	171	Placebo vs. sunitinib	5.5 vs. 11.4	<0.001
Caplin et al. (CLARINET)	54	2014	204	Placebo vs. lanreotide autogel	18 vs. NR	<0.001
Yao et al. (RADIANT 4)	70	2016	302	Placebo vs. everolimus	4.3.9 vs. 11	<0.001
Yao et al. (SWOG S0518)	57	2017	427	Interferon+octreotide vs. bevacizumab+octreotide	15.4 vs. 16.6	0.55
Strosberg et al. (NETTER 1)	74	2017	230	High-dose octreotide vs. octreotide + PRRT	8.4 vs. NR	<0.001
Kuntz et al. (ECOG E2211)	67	2018	144	Temozolomide vs CAPTEM	14.4 vs. 22.7	0.023

PFS progression-free survival, *NR* not reached

9.3 Targeted Therapy

Everolimus, a mTOR pathway inhibitor, is approved for advanced, progressive, well-differentiated, non-functioning GEP-NETs. RADIANT 3 trial randomized 410 patients with low-intermediate grade pNETS to 10 mg everolimus versus placebo and revealed significant improvement in PFS with everolimus (11 months vs. 4.6 months; $p < 0.001$). Other studies (RADIANT 2, RADIANT 4) also observed the same results with everolimus. Because of the significant adverse effects (neutropenia, infections, rash, diarrhea, and hyperglycemia), everolimus is currently reserved/used for patients with significant progression of disease on other modalities [67–69]. Sunitinib, a tyrosine kinase inhibitor, is also approved for use in advanced PNETs. Raymond et al. randomized 171 patients of advanced PNETs into Sunitinib 37.5 mg versus placebo. Median PFS was significantly better with sunitinib (11.4 months vs. 5.5 months; $p < 0.001$) [70]. Usually, both everolimus and sunitinib are commonly used after the progression of SSA and chemotherapy.

9.4 Peptide Receptor Radionuclide Therapy (PRRT)

PRRT is a form of systemic radionuclide-based treatment using the abundance of SSTRs expression (specifically SSTR2) in NETs, to act against NETs. Yttrium-90 (90Y) and Lutetium-177 (177Lu) are the most commonly used radioisotopes for this purpose with reported response rates of 4–38% and 31–55% respectively [71, 72]. Commonly observed side effects with PRRT are nephrotoxicity (90Y > 177Lu), bone marrow insufficiency, myelodysplastic syndrome, and leukemia. Recently, a phase III, randomized control trial, NETTER-1, tested PRRT + octreotide versus high-dose octreotide in patients with advanced, SSTR-positive, midgut NETs who progressed on standard-dose octreotide LAR. Investigators reported a 79% reduction in risk of progression or death with a combination of PRRT+ octreotide ($p < 0.001$) and the trend towards improved overall survival. PRRT with ^{177}Lu-DOTATATE is generally well tolerated, with the commonest adverse events being renal insufficiency (0.4–1.9%) and bone marrow suppression (9.5–11%). Currently, PRRT is approved for use in advanced SSTR +ve, well-differentiated GEP-NETs [73]. Another emerging strategy in higher grade (G2- G3) GEP-NETs, is to combine the use of Capecitabine + Temozolomide chemotherapy with PRRT (chemo-PRRT), with the hypothesis of radio sensitizing action of chemotherapy, this approach is still investigational [74].

9.5 Liver-Directed Therapy

The liver is the most common site of metastatic disease in GEP-NETs. If complete removal of primary as well metastatic disease is feasible, resection is the first choice of treatment in metastatic liver disease. When R0 resection is not possible, liver-directed therapy in the form of transarterial chemo-embolization (TACE), transarterial radio embolization (TARE), and thermal ablation (radio frequency and microwave) are commonly used techniques for the treatment of liver lesions. Liver transplantation has also been successfully used for curative intent treatment in liver-limited metastatic disease. However, there is no level 1 evidence to support the superiority of liver transplant over debulking or medical treatment, also the indications are not well defined. With current available evidence liver transplant can be offered in liver-limited metastatic GEP-NETs of well-differentiated histology and lower grade. Patient age < 55 years, <50% liver involvement, and stable disease after resection of primary are associated with favorable outcomes [75, 76].

10 Follow-Up

Grade 1 GEP-NETs are followed every 6 months and Grade 2/3 GEP-NETs are followed every 3 months. Radiological tests and tumor markers are advised as per the site, stage, and grade of the tumor. For advanced and non-resectable or metastatic GEP-NETs with stable tumors, 6-month intervals are sufficient.

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Rectal Cancer

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Abbreviations

AAR	Age-adjusted annual incidence rate
APR	Abdominoperineal resection
CECT	Contrast-enhanced CT
CRC	Colorectal cancer
CRM	Circumferential resection margin
DFS	Disease-free survival
DRE	Digital rectal examination
EUS	Endorectal ultrasound
FAP	Familial adenomatous polyposis
HNPCC	Hereditary non-polyposis colon cancer
ISR	Intersphincteric resection
LARC	Locally advanced rectal cancer
LFT	liver function test
LR	Local recurrence
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NA	Neoadjuvant
NACTRT	Neoadjuvant chemoradiotherapy
NART	Neoadjuvant radiotherapy
OS	Overall survival
QOL	Quality of life
RFT	Renal function test
TaTME	Transanal total mesorectal excision
TME	Total mesorectal excision
TNT	Total neoadjuvant therapy
W&W	Watch-and-wait

1 Introduction

The incidence of colorectal cancer in India seems to be rising based on hospital registrations. Besides the growing population, other factors like westernization, obesity, and possibly environmental factors may account for this. The rectal cancer management has seen tremendous change over the last few decades. This chapter includes clinical presentation, diagnosis, and current evidence-based management of rectal cancer.

2 Incidence and Epidemiology

As per GLOBOCAN 2018 data, over 1.8 million new cases and 881,000 deaths are estimated to occur in 2018 due to colorectal cancer [1]. Colorectal cancer is now the third most common cancer worldwide in incidence (10.2%). It is the second most common cancer responsible for 9.2% of all cancer deaths. India belongs to countries that are known to be less prevalent for colorectal cancer. But recent years have shown an increase in the incidence rate for colorectal cancer in India. In India, the age-adjusted annual incidence rates (AARs) for colon cancer and rectal cancer in men are 4.4 and 4.1 per 100,000, respectively. The AAR for colon cancer in women is 3.9 per 100,000. As per the national cancer registry program document projected case burden in 2020 for colon and rectum cancer is 51,906 and 46,247, respectively [2]. This rising trend in colorectal cancer is attributed to a change in lifestyle, obesity, etc. Recently a trend has shown a higher incidence of colorectal cancer in young patients and India is no exception to this. A recent retrospective study done at TMC (Tata Memorial Centre) over a year has shown 45.1% of patients are below 45 years of age [3]. While partly contributed by the population pyramid, the reasons for this trend are still unknown.

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3 Clinical Presentation

Clinical presentation of rectal cancer mimics benign conditions like hemorrhoids and is often misdiagnosed by local practitioners. A thorough history and proper physical examination including a rectal examination are paramount for early diagnosis of rectal cancer.

Bleeding per rectum is the most common symptom of rectal cancer. Change in bowel habits persisting for more than 6 weeks, unexplained iron deficiency anemia, and significant weight loss are other alarm symptoms that merit urgent investigation.

Spurious diarrhea is the next common symptom. The feeling of incomplete evacuation and tenesmus is common in low rectal cancer. Large or structuring tumors may present with obstruction.

Colicky abdominal pain and bloating sensation are caused by partial bowel obstruction. Lower back pain occurs in locally advanced rectal cancer due to the involvement of nerve trunks.

Other rare manifestations include jaundice due to extensive liver metastases, abdominal distention due to ascites, peritonitis due to perforation, etc.

4 Evaluation and Work-up

4.1 History

Detailed family history should be taken from a patient. Significant family history of familial adenomatous polyposis (FAP) *and* hereditary nonpolyposis colon cancer (HNPCC) necessitates genetic counseling with further investigations.

4.2 Digital Rectal Examination

Digital rectal examination (DRE) confirms the diagnosis, location, and nature of the lesion with high predictive value. High rectal or rectosigmoid lesions are not palpable on per rectal examination. A rigid sigmoidoscopy can examine the rectum for up to 15 cm and is used for accurate location of the lower end of the tumor. Distance from the anal verge gives a good idea about surgical planning and anal canal preservation.

4.3 Biopsy

Histopathological confirmation can be done with proctoscopy or rigid sigmoidoscopy for low rectal lesions or with colonoscopy-guided biopsy for the upper rectal lesion. Any suspicious lesion in another part of the colon should be biopsied. It should be noted that adenocarcinoma of the rectum has three different categories adenocarcinoma, mucinous tumors, signet with different biology, and different responses to chemoradiation [4].

4.4 Blood Investigations

It includes hemogram (CBC), renal function tests (RFT), liver function tests (LFT), and tumor markers (serum CEA and Serum CA 19–9).

Tumor markers levels should be obtained in all patients in the preoperative and postoperative periods. If a previously normalized tumor marker level increases in post-surgery follow-up, it indicates recurrence. Very high tumor markers level indicates advanced metastatic disease [5].

4.5 Colonoscopy

Synchronous colorectal tumors are seen in 2–6% of patients. Synchronous adenomatous polyps are seen in 30% of patients. A complete colonoscopy should be done in all patients to rule out any synchronous lesions in the colon. If colonoscopy is incomplete before surgery, it should be done at 6 months post-surgery. However, the incidence of polyps is relatively low compared to the Western population. A study done over a year in 800 patients at Tata Memorial Hospital has shown 1.4% synchronous malignancies and 9% synchronous polyps [6].

4.6 Radiological Examinations

The following are the investigations done for the diagnosis and staging of rectal cancer:

- Contrast-enhanced CT scan (CECT) (thorax+abdomen+pelvis)
- Magnetic resonance imaging (MRI) (pelvis)
- Endorectal ultrasound (EUS)
- Staging laparoscopy (for near obstructing tumors)

CECT and MRI are essential tests.

CT scan of the thorax is preferred over a chest X-ray as it has more sensitivity and specificity. A recent study at TMC has shown CT chest for staging compared to x-ray chest led to more referrals for pulmonary metastasectomy, the outcome of patients detected with CT was better compared to those detected with x-ray chest alone [7]. CT scan of the chest and abdomen looks for metastatic disease to the liver, lung, retroperitoneal lymph nodes, peritoneal cavity, and

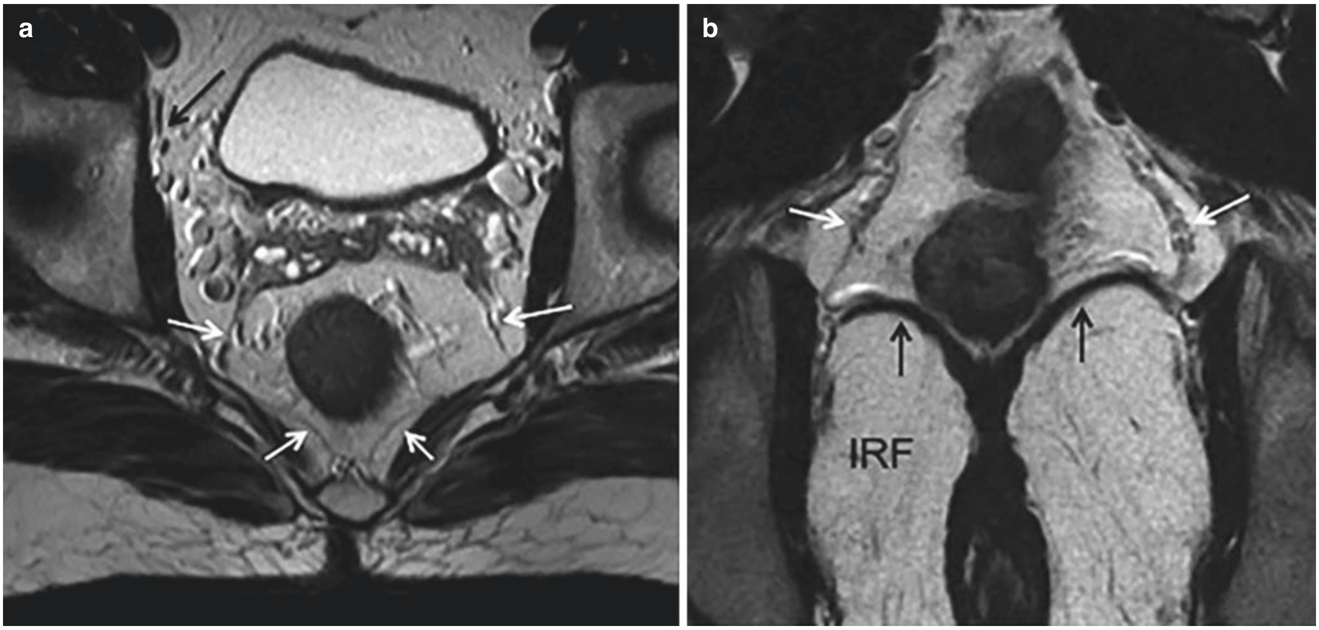

Fig. 1 (**a**) Axial T2W MRI and (**b**) coronal T2W MRI. White arrows show mesorectal fascia (MRF). The black arrow in (**a**) shows obturator vessels. Vertical arrows in (**b**) show the levator ani, forming the roof of the ischiorectal fossa (IRF). MRF thins out as it reaches the levator ani. Images courtesy of Dr. Supreeta Arya

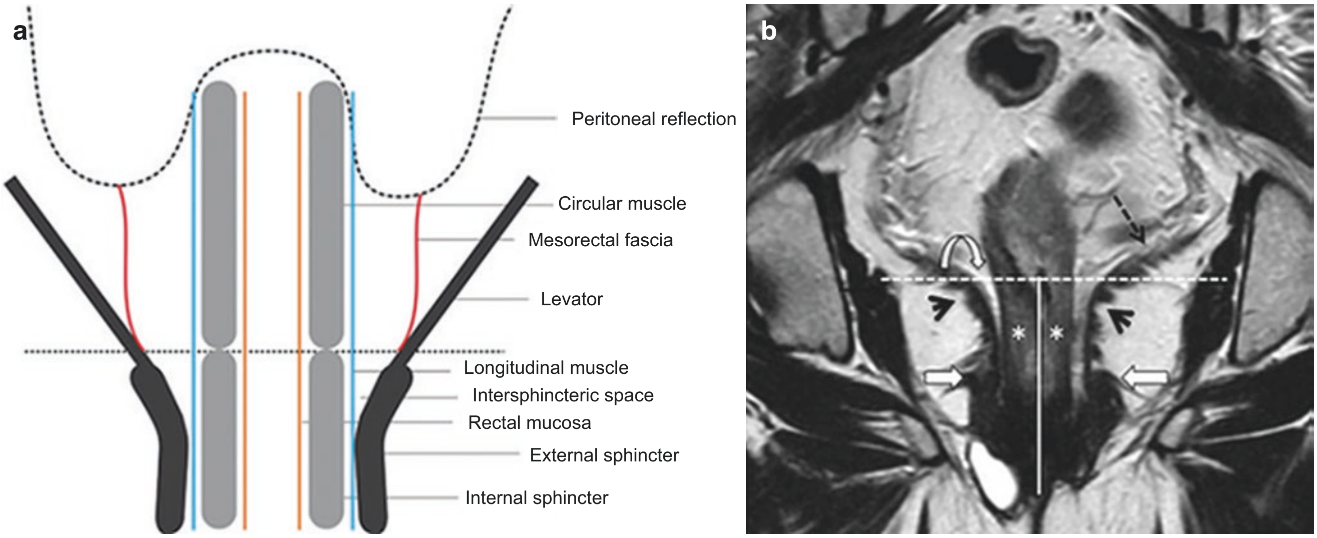
a
Peritoneal reflection
Circular muscle
Mesorectal fascia
Levator
Longitudinal muscle
Intersphincteric space
Rectal mucosa
External sphincter
Internal sphincter
b
*
*

Fig. 2 (**a**) Levator–sphincter complex. (**b**) Coronal T2W MRI. Levator ani (dashed arrow) inserting into puborectalis (arrowhead); anorectal junction (horizontal line); anal canal (vertical line); internal sphincter (*); inter-sphincteric space (curved arrow). Black arrows show the thickest part of the external sphincter (continuous with puborectalis above). Images courtesy of Dr. Supreeta Arya

other organs. If contrast is contraindicated, MRI without contrast or PET CT can be done.

Pelvic MRI for local staging is mandatory for patients who are a candidate for resection. Those patients with an extensive metastatic disease, where resection is not an option don't require pelvic MRI. Pelvic MRI assess T and N stage more accurately than CT scan, more important, mesorectal fascia can be seen only on MRI (Fig. 1). Rectal MRI includes T2 weighted images non-contrast, with axial sections perpendicular to the rectum without endorectal coil using either 1.5 or 3-Tesla scans. This helps in planning neoadjuvant therapy, response to neoadjuvant therapy, and plans of surgery (Intersphincteric resection, APER, extra-levator APER, exenteration), it also helps plan whether the anastomosis can be stapled or needs handsewn anastomosis (Figs. 2 and 3) [8]. MRI helps in identifying mesorectal fascia, involvement of mesorectal fascia, and

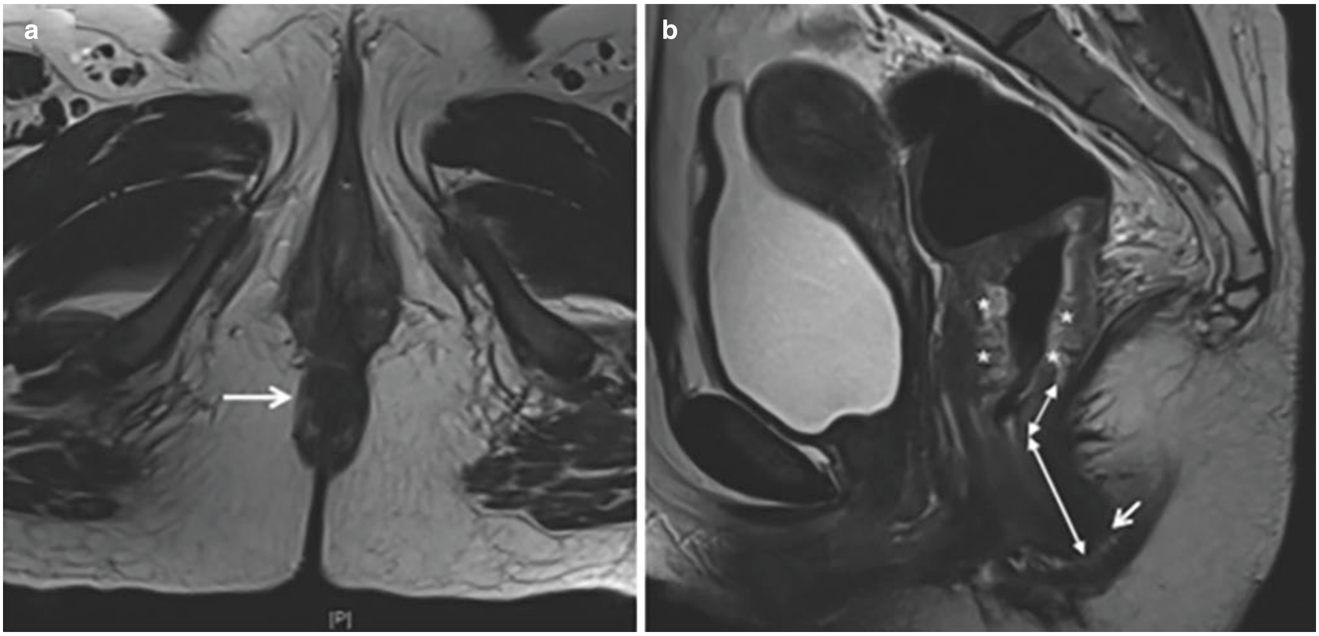

Fig. 3 (**a**) Axial T2W MRI showing anal verge (arrow). (**b**) Sagittal T2W MRI shows circumferential mid-lower rectal tumor (*). The arrow shows the anal verge. Double-ended arrows show the measurement of the distance of the lower limit of the tumor from the anal verge. Images courtesy of Dr. Supreeta Arya

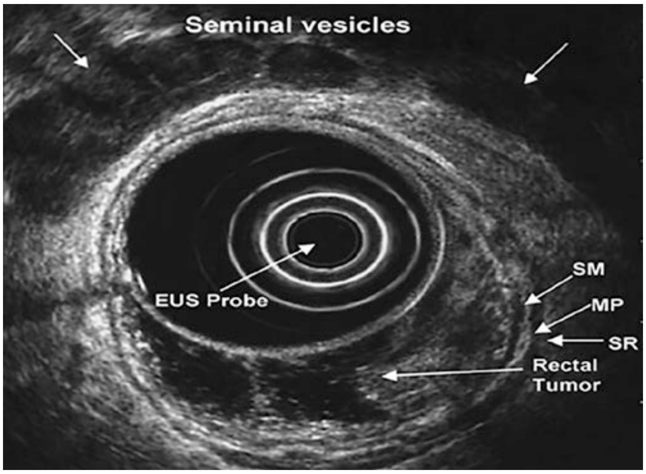

Fig. 4 EUS image of T1 rectal cancer confined to mucosa and superficial submucosa. *SM* submucosa, *MP* muscularis propria, *SR* serosa

extra-mesorectal nodes. MRI, however, cannot differentiate between T1, and T2 cancers, and endoanal USG is used to identify T1 patients suitable for local transanal resection or TEM (transanal endoscopic microsurgery) (Fig. 4) [8].

PETCT is routinely not indicated. It should be used in a patient with oligometastatic disease who is treated with curative intent, where it may change management in 8% of cases [9] when CT/MRI has equivocal findings or a patient with a contraindication to IV contrast agent. It is also recommended for rising CEA on surveillance scans compared to routine CT scans.

Staging laparoscopy in near obstructing rectal cancers for creating stoma detects peritoneal metastases and liver metastases not seen on a scan and changes management in more than 20% of cases [10].

4.7 Staging

For staging kindly refer to the AJCC (eighth edition) staging classification for rectal carcinoma [11].

5 Management of Rectal Adenocarcinoma

Outcomes of rectal cancer have improved with increased uptake of total mesorectal excision (TME), MRI for preoperative staging, and neoadjuvant chemoradiotherapy. Management of disease changes as per clinico-radiological staging of disease. Rectal cancer management should be discussed in a multidisciplinary meeting that includes the surgical oncologist, medical oncologist, radiation oncologist, radiologist, and pathologist.

5.1 T1, T2, N0, M0 (MRI Cannot Differentiate Between T1/T2 Cancer, and EUS is Used to Confirm T1 NO Disease)

The following are surgical options available for early-stage rectal cancers:

- Local excision.
- Transabdominal resection.

Early-stage rectal cancers are now diagnosed on screening colonoscopies increasingly. T1 and T2 lesions are accurately diagnosed with MRI pelvis and EUS examinations preoperatively. For these early tumors nowadays, there is greater acceptance for less invasive surgery. We have understood now that tumor biology and risk factors for aggressive disease are the main factors responsible for the prognosis of these lesions. T1 lesions with favorable features have <10% risk of nodal metastases [12, 13].

The following are local options available for early rectal cancer:

- TAE (transanal excision).
- TEM (transanal endoscopic microsurgery).
- TAMIS (transanal minimally invasive surgery).

The advantages of local excision are low morbidity, rapid recovery, and less sphincter dysfunction while disadvantages include more vigilance and risk of recurrence. The local recurrence rate varies from 0–40%.

Criteria for transanal excision:

- T1, SM1 lesions (incidence of lymph node metastasis less than 5%).
- Small lesions (<3 cm).
- Occupying less than the third circumference.
- Low-grade tumors, well to moderately differentiated.
- Within 10 cm from the anal verge.
- Preferably superficial, mobile, polypoidal lesions.
- No e/o enlarged lymph nodes.

5.1.1 TEMS

This is another form of local excision that uses a special type of proctoscope through which dissecting instruments are maneuvered after carbon dioxide insufflation. The advantage of TEM over conventional TAE is that high rectal lesions can be excised with good accuracy. An indication of TEMS is the same as TAE described above. There is a significant learning curve for TEMS.

5.1.2 TAMIS

Atallah et al. described this new technique with the advantages of wider application in the rectum, lesser compromised margins, and low recurrence rates [14]. SILS Port and the GelPOINT Path are the platforms used for this procedure. Pneumorectum is achieved with a more advanced AIRSEAL system. The laparoscopic instrument required is a long 5 mm camera, a grasper, electrocautery, needle drivers, etc. Intraoperative complications are bleeding and entry into the peritoneal cavity. Later complications are rectal stenosis and rectovaginal fistula. There is limited data available for early rectal cancer resection by the TAMIS method. The local recurrence rate varies between 3–9%.

Salvage TME (total mesorectal excision) resection is a standard option in case of local recurrence and adverse TNM features on histopathology.

5.2 T3, N any, M0

It is a consensus that T3, N0, and T1–3, N+ patients should receive neoadjuvant chemoradiotherapy (NACTRT) followed by surgery and then systemic chemotherapy. However, unlike the NCCN mercury group believe that since a T3 tumor (T3A, B) with free CRM and nodes not touching CRM do not impact local recurrence, they can be operated upfront [15]. However, this is not universally accepted. In such cases, we advocate short-course radiotherapy. Surgery of the rectum was revolutionized by a concept of total mesorectal excision (TME). TME involved dissection along the mesorectal fascia to remove the mesorectum completely leading to a significant decrease in local recurrence.

Postoperative chemoradiotherapy has shown a decrease in the risk of recurrence historically (NSABP R-01) [16]. Now there is robust data that show that preoperative chemoradiotherapy significantly downstages a tumor and decreases the local recurrence rate though there is no difference in overall survival (OS).

Principles of surgery:

- Transabdominal resection involves the following types of surgery (Figs. 5 and 6).

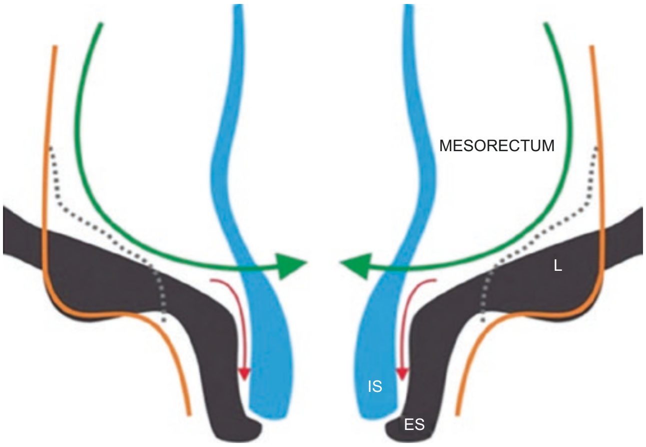

Fig. 5 Incision lines for surgical procedures: Anterior resection (green); Intersphincteric resection (red), APR (dotted), extra levator APR (orange). The sphincter is removed in the latter two surgeries. *ES* external sphincter, *IS* internal sphincter. Images courtesy of Dr. Supreeta Arya

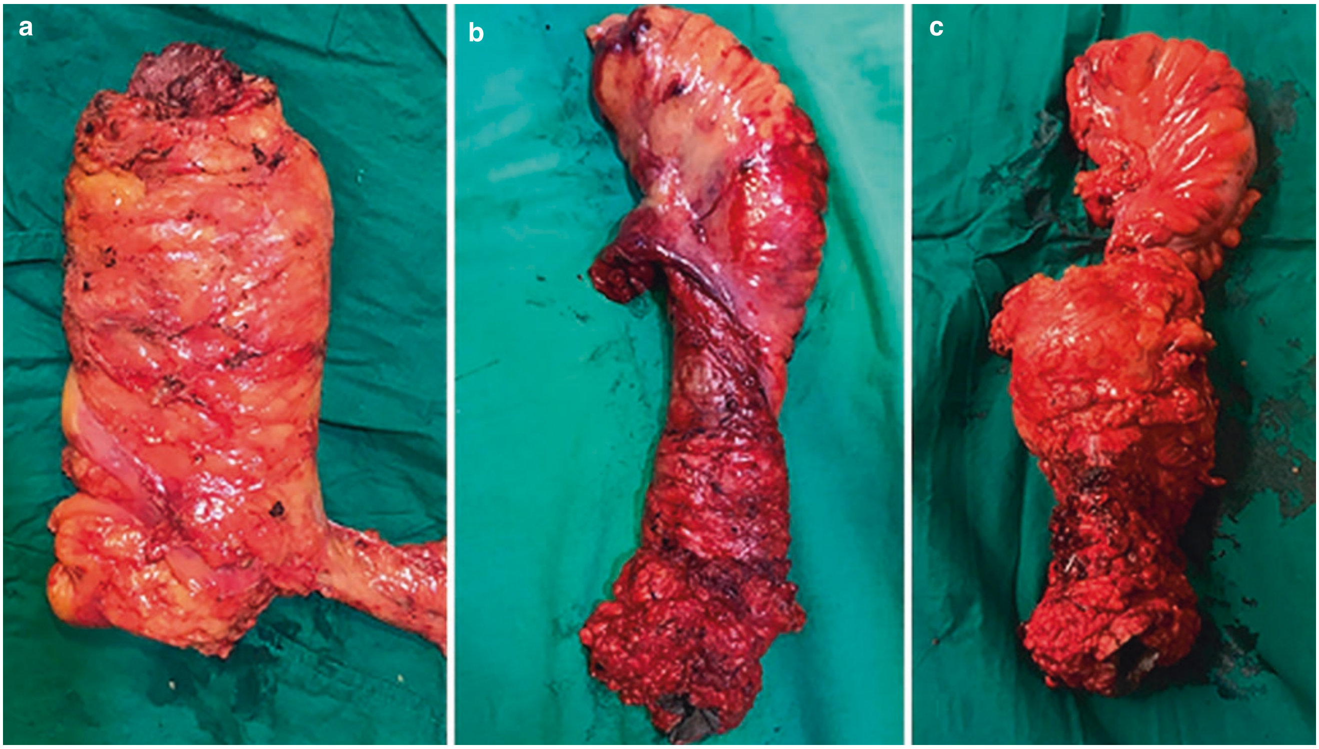

Fig. 6 TME specimen of (**a**) ISR, (**b**) APR, and (**c**) pelvic exenteration

  - Low anterior resection (LAR)
  - Intersphincteric resection (ISR)
  - Abdominoperineal resection (APR)
- Presurgery diversion stoma: Those patients with acute/subacute intestinal obstruction and long-segment disease should undergo diversion stoma. It improves the patient's oral intake and overall nutrition. Pre-operative stenting in near obstructing, obstructive tumors is not recommended as the incidence of procedure-related perforation/ disease's free survival is lower in stented patients [17].
- Surgery should be done 8–12 weeks after a full course of chemoradiation [18].
- After SCRT (short course radiotherapy) surgery can be done immediately after 1 week or after 8–12 weeks.
- A tumor should be excised with adequate margins.
- The proximal margin of 5 cm and distal margin of 5 cm for upper rectal tumors (tumor-specific mesorectal excision), for mid and low rectal cancer, complete TME with 1 cm distal margins is ideal.
- The distal margin should be confirmed tumor-free with a frozen section intra-operatively when possible.
- Total mesorectal excision (TME) is a standard of practice and decreases local recurrence.
- Abdominoperineal resection with a permanent colostomy should be done in patients with levator ani, external sphincter involvement on MRI.
- In APR, the tumor specimen should be cylindrical and one should avoid 'waisting' of the specimen (extra levator APR technique).
- ISR is feasible in those patients with free Intersphincteric space on MRI and good anal sphincter tone.
- Covering diversion ileostomy is preferred in all patients who receive NACTRT, low coloanal anastomosis, and ISR.
- Lymph node dissection: lateral pelvic lymph node dissection is generally done in only those patients in which MRI shows enlarged extra mesorectal nodes after chemoradiotherapy.

5.3 Laparoscopic Versus Open Approach

Open TME resection has been a standard surgical approach in rectal carcinoma. The last two decades have seen a tremendous evolution in minimally invasive techniques. There was concern about minimally invasive approaches regarding complete oncological clearance. Randomized trials have shown that the laparoscopic approach is equivalent to the open approach along with less perioperative morbidity.

The first randomized trial was a CLASICC trial in which 794 patients were randomized for laparoscopic and open approach involving both colon and rectal cancer patients

[19]. Primary short-term endpoints were circumferential and longitudinal margins and in-hospital mortality. CRM (circumferential resection margin) positivity was significantly higher in the laparoscopic group for rectal anterior resection than the open group. It was concluded that laparoscopic resection should not be used routinely. Further long-term studies of CLASICC trial patients have shown no difference in local recurrence, overall survival (OS), and disease-free survival (DFS) [20].

Two other trials COLOR II and COREAN have shown similar results in recurrence, DFS, and oncological outcomes confirming the safety of the laparoscopic approach [21, 22]. COLOR II trial has shown blood loss and postoperative recovery was better in the laparoscopic group. There was no difference between oncological clearance, positive CRM, or distal resection margin between the two groups. Also, mortality within 28 days showed no difference. There was no difference in DFS between the two groups (laparoscopic 74.8% vs. open 70.8 at 3 years). The author concluded that laparoscopic surgery is equivalent in safety with rapid recovery in selected patients treated by skilled surgeons. COREAN trial included 340 patients with mid and low rectal cancer after chemoradiotherapy. There was no difference between the two groups regarding safety, CRM, the number of harvested nodes, and perioperative morbidity. 3-year DFS was 72.5% vs. 79.2% for open and laparoscopic groups, respectively.

Recent two trials (ACOSOG Z6051 and ALaCaRT) which were designed to see non-inferiority of laparoscopic surgery have given controversial results. Both trials have failed to show non-inferiority [23, 24]. In the ALaCaRT trial, successful resection was done in 194(82%) and 208 (89%) for laparoscopic and open groups respectively. CRM was free in 93% of patients in the laparoscopy group and in 97% who underwent open surgery. The distal margin was free in 99% of cases in both groups, and TME was complete in 87% of patients in the laparoscopic surgery group and 92% in the open surgery group. The authors concluded that for patients with T1-T3 rectal cancer, noninferiority of laparoscopic surgery for successful resection is not established. Also, in spite of good quality surgery, it does not provide sufficient evidence for routine use of laparoscopic surgery. Similar evidence was found in the ACOSOG Z6051 trial. 81.7% and 86.9% of patients underwent successful resection in laparoscopic and open groups respectively. This trial did not support the non-inferiority. However, proponents of laparoscopic cite low patient numbers and the use of composite score CRM and DRM (distal resection margin) as a drawback of this study. Near-complete TME and incomplete TME were put in one group, whereas the outcome of complete and near-complete TME is not much different. The 2-year follow-up of this study did not show an inferior outcome in the laparoscopic group (similar to long-term outcomes of MRC Classic (ASOCOG 2018) [25].

The most recent analysis which includes 14 RCT (randomized controlled trials) with 4030 patients has been published in February 2017 [26]. It has concluded, a significantly higher risk of noncomplete resection in patients with laparoscopic resection than open resection. These results questioned the oncologic safety of laparoscopy for the treatment of rectal cancer. However, the long-term results of the MRC CLASICC, COLOR 2 trial, and the 2-year follow-up of ACOSOG did not find any difference in local recurrence disease-free and overall patient survival (Tables 1, 2, and 3).

Table 1 Multicentric randomized trials on laparoscopic rectal cancer resection

Protocol	Years	Number of patients	Distal margin	Completeness of TME	CRM	Long-term recurrence
CLASSIC [18]	1996–2002	794	Yes	No	Yes	Yes
COLOR II [20]	2004–2010	1103	Yes	Yes	Yes	Yes
COREAN [21]	2006–2009	340	No	Yes	Yes	Yes
ACOSOG Z6051 [23]	2008–2013	486	Yes	Yes	Yes	No
ALaCaRT [22]	2010–2014	475	Yes	Yes	Yes	No

Table 2 Comparative analysis of major trials

Study	Primary site	Type of study	Lap conversion rate	Type of surgery	No.	Blood loss	Hospital stay	Leak rate
Van der pas et al. 'COLOR II' [20]	Rectum <15 cm	RCT	17%	Lap	763	200	8	13%
				Open	364	400	9	10%
Kang et al. 'COREAN' [21]	Rectum <9 cm	RCT	1.2%	Lap	170	200	8	1.2%
				Open	170	217	9	0%
MRC CLASSIC [18]	Colon + rectum	RCT	30%	Lap	268	–	10	7%
				Open	526	–	13	10%

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				Open	170	217	9	0
MRC CLASICC [18]	Colon + rectum	RCT	30%	Lap	268	–	9	7
				Open	526	–	11	1%

6 Role of Robotic Surgery in Rectal Cancer

With recent advances in robotics, robotic surgery has shown benefits in terms of vision, precision, and accuracy. Three-dimensional views, seven degrees of freedom, intuitive motion, and tremor filtration offer advantages to surgery as well as to the surgeon. Robotic rectal cancer surgery has great advantages in pelvic rectal surgery, especially in the narrow male pelvis with better-magnified vision and greater dexterity. Precise TME dissection with preservation of the hypogastric nerve with accuracy is possible with robotic surgery. Many retrospective studies and meta-analyses have shown equivalent outcomes as compared to laparoscopic surgery. The recent Robotic versus Laparoscopic Resection for Rectal Cancer (ROLARR) trial has been published [27]. It randomized 471 patients from 29 centers in 10 countries. The primary endpoint of this study was conversion to open laparotomy and similar in both groups (12.2% vs. 8.1%). A study shows no difference in conversion rate (unadjusted risk difference 4.1, −1.4 to 9.6; $P = 0.16$). Besides, no significant differences were seen in TME completion, CRM positivity, rates of intraoperative complications, postoperative complications, or 30-day mortality. There is improvement in conversion rates for robotic surgery versus laparoscopic surgery in men (odds ratio 0.455, 0.209 to 0.987; $P = 0.0429$), obese patients, and low rectal cancer. Robotic surgery provides greater benefits than laparoscopy in the narrower male pelvis. The authors concluded for surgeons with varying workload robotic surgery does not show any advantage over laparoscopy, however, with the learning curve effect, high-volume surgeons may have benefited from robotics.

At Tata Memorial Centre, a propensity cross-match analysis comparing robotic TME and laparoscopic TME has shown no difference in oncological clearance and short-term outcomes between the two groups. Also, this study shows significantly lower anastomotic leak rates and Grade III complications in robotic TME compared to initial laparoscopic rectal surgery (9.5% vs. 1.2%: $p = 0.016$) and (13.1% vs. 4.8%: $p = 0.034$), respectively [28].

7 Transanal Total Mesorectal Excision (TaTME)

Surgery for distal rectal cancer is challenging with a high CRM + ve rate (10%), local recurrence, high morbidity (anastomotic leak rates), and high stoma rates. Abdominal TME is associated with technical constraints viz., difficult visualization of anterolateral planes, neuro-vascular bundle due to difficult angle, posterior dissection requiring lifting and traction, and difficulty in determining DRM which becomes worse in the small narrow pelvis, obese patients, bulky tumor and post-RT fibrosis. Rectal cross stapling often requires 2 or 3 cartridges and hence is associated with high leak rates.

TaTME is combining of transabdominal and transanal approaches to achieve TME. The distal(horizontal) part of the dissection transanally using gel port and laparoscopic instruments enables direct visualization of the distal margin, optimal visualization of the distal TME plane, and better visualization of neurovascular bundles ventrally. Possible benefits include reduced CRM + ve rate, completeness on TME, better sexual function, and lower stoma rate.

Another potential benefit of TaTME is better anastomosis using a double purse-string technique which avoids dog ears (as opposed to LaTME) and crossing of stapler lines, resulting in lower leak rates. Evaluation of the anastomotic line is possible both by direct visualization and reverse leak test using pneumoperitoneum with the option of transanal suture reinforcement.

A systemic review comparing TaTME and laparoscopic TME(LaTME) by Deijen et al. showed a lower CRM positivity rate (3.2% vs. 7.6%) and an increased rate of complete TME (82.8% vs.75.2%) [29]. Pontallier et al. evaluated the functional outcome post-TaTME vs. LaTME and found similar bowel function (LARS score and Wexner score), similar urinary function (IPSS score) but better sexual activity [30]. The reduced need for diversion stoma was reported by Blok et al. with better QOL (quality of life) and lower cost with this approach [31].

A recent survey conducted in Norway has raised serious concerns over the results of TaTME. Out of 157 patients who were operated for TaTME, the local recurrence rate was 11.6% compared to 2.4% in Norwegian colorectal cancer registry patients ($p > 0.001$). anastomotic leak rate was 8.4% vs. 4.5% ($p = 0.047$). Due to these unfavorable rates, TaTME has been suspended in Norway [32].

The TaTME approach is not easy and requires advanced laparoscopic skills, and proper training with a long learning curve. A comparison of laparoscopic vs. transanal TME is being tested in the COLOR III trial.

8 Role of Radiotherapy

The treatment of rectal cancer has changed over time with the introduction of total mesorectal excision (TME), preoperative MRI, the concept of circumferential resection margin (CRM), and neoadjuvant radiotherapy (NART). The majority of trials have shown a decrease in local recurrence (LR) with RT either preoperatively or postoperatively. There has been a paradigm shift in the administration of radiotherapy from adjuvant to neoadjuvant (NA) setting in the treatment of locally advanced rectal cancer (LARC).

8.1 The Rationale Behind Pre-operative RT

The use of pre-operative RT has improved response rates due to the intact blood supply, improved resectability, sterilization of margins, downsizing of a tumor, improved negative CRM(R0) resection rates, increased likelihood of sphincter preservation, pathological complete response(pCR) and better treatment tolerance. Tumor downsizing in turn aids in the easy firing of surgical staplers intra-operatively which is particularly important for low rectal tumors close to the sphincter complex.

8.2 Preoperative RT vs. Surgery Alone

Systemic reviews and meta-analyses have shown decreased LR after RT. A meta-analysis of 11 RCTs by Camma et al., showed significantly lower 5-year LR (OR + 0.49; $p < 0.001$) when preoperative RT was given [33].

8.3 Pre-operative vs. Post-operative Long-Course Chemoradiotherapy

Major trials comparing pre-operative versus post-operative RT favor the use of the pre-operative approach. In the German Rectal Cancer Study Group trial, Sauer et al. randomized 823 patients (T3/4 or N+) into pre-operative long-course chemoRT (NACT-RT) (5040 cGy/28 fractions with 5-FU 1000 mg/m^2/day continuous infusion during week 1 and 5 of RT) and similar post-operative regimen (Tables 4 and 5) [35]. The NACT-RT arm reported significantly lower LR (6% vs. 13%; $p = 0.006$) and higher sphincter preservation rate (39% vs. 19%; $p = 0.004$) with no significant difference in OS. No other trial, however, has shown increased sphincter preservation after CTRT. However, sphincter preservation may increase after CTRT, decrease tumor size to enable stapling, or complete response after CTRT may enable a wait-and-watch protocol.

The Swedish Rectal Cancer Trial randomized 1168 patients to receive either 1 week of RT followed by surgery or surgery alone [36]. After a median follow-up (mFU) of 13 years, patients in the NART arm had lower LR (9% vs. 26%, p 0.001) and prolonged overall survival (OS) (38% vs. 30%, $p = 0.008$). The reduction in LR was observed at all tumor heights, although it was not statistically significant for tumors greater than 10 cm from the anal verge. This trial was, however, done in a pre-TME era.

The Dutch trial, a multi-centric RCT randomized 1861 patients to short-course RT(SCRT), 5Gyx5days followed TME vs. TME alone [34]. Local recurrence (LR) was significantly lower in the SCRT group (5% vs. 11%; $p < 0.001$) with no difference in OS after a mFU of 12 years. Similar results were demonstrated in the Stockholm II trial with lower pelvic recurrence in the SCRT group without any survival advantage [37] (Table 5).

In a meta-analysis by Loos et al., preoperative RT harmed long-term anorectal function but did not significantly affect sexual and urinary function [38].

In another study, MRCCR07 randomized 1350 stage III, rectal cancer patients, into either SCRT followed by TME or surgery followed by selective postoperative chemoRT. SCRT group had decreased LR (4.4% vs. 10.6%; $p = 0.0001$) with similar OS [39].

8.4 Indications for Neoadjuvant RT

Upper rectal cancers above the peritoneal reflection do not benefit from preoperative SCRT or NACT-RT and should be

Table 4 Sphincter preservation rate: German Rectal Cancer Study Group trial

Variable	Preoperative chemoradiotherapy ($N = 415$)	Postoperative chemoradiotherapy ($N = 384$)	*p*-value
Abdominoperineal resection deemed necessary- no (%)	116(28)	78(20)	
Sphincter preserving surgery performed- no./total no (%)	45/116(39)	15/78(19)	0.004

Table 5 RCTs comparing up-front surgery vs. SCRT f/b surgery

Trials	Design	No	FU	LR	OS
A Swedish study [36] (pre-TME-era)	SCRT à surgery vs. up-front surgery	1168	13 years	9% vs. 26%, $p < 0.001$	38% vs. 30%, $p = 0.008$
A Dutch study [34]	SCRT à TME vs. up-front TME	1861	12 years	5% vs. 11%, $p < 0.001$	50% vs. 40%, $p = 0.032$
MRCCR07 [39]	SCRT plus surgery vs. up-front surgery and selective postop CTRT	1350	4 years	4.4% vs. 10.6%, $p = 0.001$	$p = 0.40$

treated like colon cancer. However, at TMH, with the involvement of anterior peritoneal reflection (T4) we offer CTRT, as chances of tumor perforation during surgery decrease; this, however, is being looked at in a study.

Neoadjuvant RT is indicated in:

1. >T3
2. >N0
3. Threatened CRM.
4. Low rectal cancer.

8.5 Addition of Chemotherapy to Pre-operative RT

Combining radio-sensitizing chemotherapy with pre-operative RT has radiobiological rationale with increased response rate and possible early treatment of systemic micrometastasis. A systemic review and meta-analysis which included 4 major RCTs viz., EORTC, EORTC 22921, FFCD9203, and Polish trials supported the addition of chemotherapy to pre-operative RT with significantly increased pCR($p < 0.001$) and lower LR($p < 0.001$) [40]. However, there was no difference in sphincter preservation rate, morbidity, DFS, and OS.

8.6 SCRT vs. NACT-RT

Both SCRT and NACT-RT are feasible options in rectal cancer with comparable results. European nations are a proponent of SCRT whereas the use of NACT-RT is preferred in North America. In the Polish RCT, Bujko et al. compared SCRT (5x5Gy followed by surgery within 1 week) versus NACT-RT (50.4Gy in 28 fractions and infusional 5-FU and leucovorin followed by TME 4–6 weeks later) and found no difference in LR, DFS, and OS [41] However, no pre-operative MRI was done as a part of an evaluation of rectal cancer in this study.

A similar study addressing this issue, the Trans-Tasman Radiation Oncology Group 01.04 trial reported no difference in 3-year LR in both SCRT and NACT-RT arms with similar distant recurrence rates, relapse-free survival, OS, or late toxicity [42]. This trial showed NACT-RT may be more effective in reducing LR for distal tumors. In another phase III RCT, Bujko et al. explored SCRT and consolidation chemotherapy followed by surgery and found the results comparable to NACTRT in terms of R0 resection rates, pCR, and toxicities [43].

LARC can progress on NACT-RT. As per a retrospective study conducted at Tata Memorial Hospital (TMH), poorly differentiated/signet ring (PD/SR) histology had a significantly higher rate of progression both local (32.1% vs. 5.6%, $p = 0.0011$) as well as systemic (35.7% vs. 6.9%, $p = 0.0008$) as compared to well/moderately differentiated adenocarcinoma [44]. Another study from TMH showed progression in 23% of patients with signet-ring (SR) histology on NACT-RT with additional administration of NA chemotherapy [4]. Hence, these patients need to be considered for early systemic therapy, PD/SR histology being a poor biological disease with adverse outcomes.

In TMH, we prefer SCRT in three settings viz., signet ring histology, oligometastatic disease (where early initiation of systemic therapy is warranted), and economic/logistic issues.

8.7 Optimal Interval Between Preoperative RT and Surgery

The interval between NACT-RT and surgery has been suggested to be 6–8 weeks allowing sufficient time for tumor downsizing, facilitating surgery, and improved pCR rates whereas, after SCRT, the surgery is in the following week [18].

It has been shown that delaying surgery more than 6–8 weeks results in more pCR and pCR is related to increased survival. A retrospective study done at Tata Memorial centre has shown that delaying surgery more than 12 weeks does not increase pCR and survival [45]. A Greccar-6 randomized controlled trial randomized 265 patients into 7- and 11-weeks post-CTRT. The primary endpoint was the pCR rate. No difference was found in oncological outcomes in the two groups [46].

In a multi-centric randomized Stockholm III trial, Pettersson et al. demonstrated significant tumor downstaging if surgery was performed at 4–8 weeks post-SCRT [47]. A similar benefit was shown by Bujko et al. [48]. This supports SCRT followed by delayed surgery, an approach that is a viable option in elderly patients who are unfit for chemotherapy.

8.8 Reassessment/Response Assessment After NART

Assessment of tumor response relies on clinical examination (DRE), proctoscopy, and MRI. Appropriate surgical strategy, the type of operation, and the possibility of "watch-and-wait" strategy depend upon the above findings.

8.9 Response to Pre-operative CRT as a Predictor of Outcome

Around 15–27% achieve pCR. Maas et al. have reported improved DFS in those achieving pCR (83.3% vs. 65.6%; $p < 0.0001$). However, it has not translated into increased OS [49].

8.10 Clinical Complete Response and a "Watch-and-Wait" Approach

The "watch-and-wait" (W&W) approach was first introduced by Habr-Gama in patients with clinical complete response (cCR) [50]. Following NACT-RT, cCR can be obtained in 10%–40% of patients.

cCR is defined as follows:

1. The absence of any palpable tumor or irregularity at DRE.
2. No visible lesion at rectoscopy/sigmoidoscopy except a flat scar.
3. Telangiectasia or whitening of the mucosa.
4. Absence of any residual tumor in the primary site and draining lymph nodes on imaging with MRI or ERUS.
5. Negative biopsies from the scar and an initially raised CEA level which returns to normal (< 5 ng/ml).

Dedicated centers have reported encouraging oncological and functional outcome results with this strategy. However, a standardized strict protocol for intensive surveillance is needed.

The OnCoRe project, in a propensity-score, matched analysis, showed no significant difference in 3-year OS with the W&W approach with better 3-year colostomy-free survival than those who underwent surgical resection [51].

The International W&W database (IWWD) has been created to include the W&W registries worldwide (47 institutions across 15 countries) to define guidelines for treatment and surveillance. Long-term outcomes from IWWD in 1009 patients kept on W&W after an mFU 3.3 years revealed the 2-year cumulative incidence of local regrowth of 25.2% (95% CI 22.2–28.5%), distant metastasis rate of 8% and 5-year OS of 85% (95% CI 80.9–87.7%) [52].

W&W is still not the standard of care. At TMH, W&W is offered to patients with cCR if they agree to a close surveillance protocol with the accepted risk of LR. Usually, this approach is avoided in PD/SR histology. Triple assessment–clinical, radiological, and endoscopic evaluation is done every 8–12 weeks in a multi-disciplinary clinic comprising a team of a colorectal surgeon, radiation oncologist, medical gastroenterologist, and radiologist.

8.11 T3, N any, CRM Involved (on MRI)/T4, N Any/Locally Unresectable/Medically Inoperable

Definition of CRM involvement:

1. A tumor within 1 mm of mesorectal fascia.
2. For a lower third of a tumor within 1 mm of the levator muscle.
3. For anal canal tumors invasion into or beyond intersphincteric space.

As discussed above for locally advanced rectal carcinoma NACTRT followed by 8–12 weeks gap and surgery and is standard of care. Those patients who have CRM positive on post-NACTRT MRI should receive 12–16 weeks of chemotherapy (FOLFOX/CAPOX). Post-surgery 6 months adjuvant chemotherapy is recommended.

8.12 Role of NACTRT Followed by NACT

Studies of long-course chemoradiation followed by preoperative chemotherapy for locally advanced rectal cancer have been conducted by several groups. (Table 6) A study conducted by Ostwal et al. at TMH has shown that additional chemotherapy post-NACRT which has unresectable disease improves resection rates, survivals, and downstaging of tumours with acceptable toxicity. FOLFIRINOX (folinic aci d+5FU + irinotecan+oxaliplatin) shows improved survival over CAPOX, specifically in patients who are amenable to conservative surgery post-CRT and CT [53–55].

8.13 Role of Adjuvant Chemotherapy

In all stage II/III rectal cancer following NACTRT and surgery adjuvant chemotherapy is recommended if they did not receive neoadjuvant chemotherapy regardless of the surgical pathology results; however, few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and its role is not well-defined.

As per the initial EORTC Radiotherapy Group Trial 22,921, addition of 5-FU as adjuvant chemotherapy to NACTRT provided no benefit, however, had DFS benefit. In the long-term it did not show the OS benefit, however, had DFS benefit [56]. In the phase III ECOG E3201 trial, the effect of adding either oxaliplatin (FOLFOX) or irinotecan

Table 6 NACTRT followed by NACT approach

Study	Inclusion criteria	No.	Treatment	pCR (%)	Outcomes
Zampino, et al. [49]	T3, T4 or N+	51	ChemoRT with capecitabine → × 6 weeks	18	R0 resection—100% 5-year DFS—85.4%
Gao, et al. [50]	T4, bulky (>5 cm), <6 cm from the anal verge, N+, elevated CEA	36	ChemoRT with CAPOX→CAPOX × 3 weeks	36	R0 resection—100% Downstaged—81%

(FOLFIRI) to 5-FU/LV-based adjuvant chemotherapy, found that the FOLFOX could be safely given to the patients [57]. The role of Oxaliplatin in combination with LV/5 FU was underlined by the CAO/ARO/AIO-04 trial and the open-label Phase II ADORE [58, 59].

However, the role of chemotherapy in the adjuvant setting has been conflicting, especially when receiving preoperative treatment in stage II/III tumors. A meta-analysis of four randomized trials (1196 patients) showed that adjuvant fluorouracil-based chemotherapy (5-FU/LV, Capecitabine, or CAPEOX) after preoperative therapy and surgery in stage II/III cancers failed to improve OS, DFS, or the rate of distant recurrences in patients [60]. On the other hand, Peterson et al. in their metanalysis found support for adjuvant 5FU-based chemotherapy [61]. Also, Petrelli et al. in their metanalysis found a positive effect on disease-free survival and overall survival rates with adjuvant chemotherapy. But the evidence is poor due to the significant bias of non-randomised studies [62]. Carvalho et al. in 2017 in their metanalysis found no robust evidence for adjuvant chemotherapy [63].

Given the above conflicting results, adjuvant chemotherapy in rectal cancer remains a standard of care. The preferred regimens include FOLFOX or CAPEOX. The other options though less preferred include 5-FU/leucovorin (5-FU/LV) or Capecitabine, especially in patients whose cancer responded to neoadjuvant treatment with 5-FU or Capecitabine.

The answer to the question of the timing and duration of the therapy is based on the systematic review of a meta-analysis of 10 studies involving more than 15,000 patients done in 2011. The study showed that the OS was decreased by 14% if there is a delay of chemotherapy beyond 4 weeks [64]. So, the answer is the treatment must be started as soon as possible when the patient is medically fit preferably before 4 weeks. The duration of adjuvant therapy is again not well defined however the consensus is 6 months of perioperative therapy.

8.14 Role of Neoadjuvant Chemotherapy Followed by Chemoradiotherapy (Total Neoadjuvant Therapy Approach)

As local recurrence has decreased due to NACTRT and TME, now distant recurrence is a major concern in LARC. Neoadjuvant chemotherapy followed by NACRT is an attractive approach as chemotherapy treats micrometastatic disease and is also believed to increase the pCR rate. Preoperative chemotherapy is better tolerated than postoperative chemotherapy. As most of the data come from phase II trials there is a need to do a randomized phase III trial [65–67]. Recent NCCN guidelines have included NACTRT followed by the NACT protocol for LARC.

8.15 Role of Beyond TME Surgery

In LARC many times multi-visceral resection, pelvic exenteration, and pelvic sidewall resections are required to get R0 margins. With recent advances in neoadjuvant treatment and aggressive surgical strategy, 5-year survival has increased beyond 50%. These surgeries have considerable surgical morbidity. With recent advances in minimally invasive surgeries, these complex surgeries can be performed with less perioperative morbidity and equivalent surgical outcomes [68].

8.16 What Is an Adequate Adjuvant Treatment for Up-Front Resected Stage II, III Tumours?

NCCN guidelines recommend NACTRT for stage II, and III tumors while ESMO guidelines advocate up-front resection for T3N0 tumors without CRM involvement and extramural vascular invasion in upper and mid-rectal tumors. Traditionally, postoperative chemo-radiotherapy was recommended for all stage II-III patients (1990 national institute of health consensus). But routine use of adjuvant CTRT in low-risk cancer is debated. There are not much good quality studies on this. A study was conducted at TMH where upfront resected patients were divided into low-risk and high-risk (T4, N2, LVI/PNI+, CRM +). The study did not show any benefit of adjuvant CTRT over adjuvant CT for low-risk group patients. Thus, it seems that adjuvant CTRT can be avoided in low-risk patients [69].

8.17 T any, N any, M+

Twenty-five percent of CRC patients present with metastatic disease and 35% of patients will develop metastasis on treatment. Treatment of metastatic colorectal cancer has changed from palliative to curative in a selected group of patients. The aim of treatment in mCRC is a cure in selected patients, prolongation of survival, palliation, and increase in quality of life.

Treatment of metastatic rectal cancer generally has the following scenarios

- Limited resectable disease: surgery with perioperative adjuvant chemotherapy.
- Limited unresectable disease: Chemotherapy followed by surgery if possible.
- Widespread and aggressive disease and disease-related symptoms: palliative therapy.

Before starting treatment, it is essential to consider the following factors:

- Patient factors: General condition, emotional status, age, comorbidities, Eastern Cooperative Oncology Group performance (ECOG) status,
- Tumor factors: indolent versus an aggressive tumor, tumor load, and mutational status (RAS and BRAF).
- Treatment goals: Tumour shrinkage to achieve a radical surgery of metastases or palliation, disease control to delay progression, and worsening of the patient's general condition.

9 Treatment of Synchronous Resectable Metastatic Liver/Lung Disease

9.1 Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease

Perioperative chemotherapy is recommended in most patients undergoing liver or lung resection to eradicate the residual microscopic disease if any. The total neoadjuvant therapy (TNT) approach is recommended by the panel in 2018 for synchronous lung and liver metastases. Neoadjuvant and/or adjuvant therapy may still be considered in patients with resectable metachronous metastases. Two meta-analyses, one with 3 randomized clinical trials comparing surgery alone to surgery plus systemic therapy and the other with 10 studies with colorectal liver metastases has shown PFS benefit but not an OS benefit [70–72].

EORTC phase III study (EORTC 40983) compared chemotherapy in conjunction with surgery versus surgery alone. It showed the use of perioperative FOLFOX (6 cycles before and 6 cycles after surgery) for patients with initially resectable liver metastases demonstrated absolute improvements in 3-year PFS of 8.1% ($P = 0.041$) and 9.2% ($P = 0.025$); however, there was no OS benefit [73].

The optimal sequencing of chemotherapy remains unclear. It is recommended to use a neoadjuvant treatment approach for patients with synchronous metastases. Metachronous metastases can be treated with neoadjuvant and/or adjuvant systemic therapy.

The advantage of giving preoperative therapy include earlier treatment of micrometastatic disease; determination of responsiveness to chemotherapy, and avoidance of local therapy in those who progress early. The disadvantage includes the risk of disease progression or difficulty in identifying the areas of resection in case of complete response post-chemotherapy [74, 75] and risk of hepatotoxicity (liver steatohepatitis and sinusoidal liver injury) when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively [76–80].

To decrease the risk of hepatotoxicity, the neoadjuvant period is usually limited to 2 to 3 months. Patients should be carefully monitored by a multidisciplinary team.

9.2 Dilemma About the Sequencing of Preoperative Treatment Modalities

Various strategies have been developed with various advantages and disadvantages. Therefore, all these patients should be discussed in the multidisciplinary team (MDT) meeting so that a more accurate strategy can be determined with better results. Following are various neoadjuvant strategies:

1. Up-front chemotherapy followed by short-course radiotherapy and delayed surgery.
2. Short-course radiotherapy with subsequent systemic chemotherapy followed by delayed surgery (an approach we follow at TMH).
3. Systemic chemotherapy with intensified chemotherapy regimen in the setting of long-course chemoradiation therapy.
4. Liver-first approach (up-front chemotherapy followed by liver resection followed by CTRT followed by surgery).

10 Treatment of Patients with Limited Unresectable Disease

Neoadjuvant chemotherapy is the preferred approach. The unresectability definition is subjective and depends upon the aggressiveness of the surgeon. Chances of downstaging are 10–15%. Various reports have shown that only 12–33% of patients will have an objective response to result in R0 resection [81–83]. Radiographic response assessment should be done at 6–8 week intervals and surgery should be undertaken as soon as the metastases are resectable. If the primary is resectable, SCRT is preferred before surgery.

There are various regimens used for conversion therapy: FOLFOX, FOLFOXIRI, FOLFIRI+Cetuximab, or panitumumab for RAS, B-RAF wild type.

11 Treatment of Widespread Metastatic Rectal Cancer

Treatment of the widespread metastatic disease is similar to metastatic colon cancer and is discussed in detail in the chapter on colon cancer.

12 Management of Recurrent Rectal Cancer

Local recurrence after rectal cancer resection has decreased over the last two decades, however, in patients with locally advanced disease, recurrence after local resection occurs in 5–15% of patients. Almost half of these will present with unresectable systemic metastasis and in these cases, palliative treatment in the form of chemotherapy/radiotherapy is offered.

Selected few patients eligible for resection can undergo APER, pelvic exenteration / sacrectomy with 5-year survival over 35% if R0 resection is achieved [84, 85].

Follow-Up

1. After curative-intent surgery and adjuvant chemotherapy:

1–2 years/ 3 monthly	Sr CEA, Sr CA 19–9, clinical examination
3 year/6 monthly	Sr CEA, Sr CA 19–9, clinical examination
4/5 year/yearly	Sr CEA, Sr CA 19–9, clinical examination

CECT (Thorax+Abdomen+Pelvis): should be done yearly.

Colonoscopy: Every 1 year after surgery and every 5 years thereafter. If presurgery colonoscopy is incomplete due to obstruction then should be done at 6-month post-surgery.

PETCT: Not recommended.

Routine CEA and CT scans are not recommended after 5 years.

2. After lung/liver resection

1–2 years/ 3 monthly	Sr CEA, Sr CA 19–9, Clinical examination
3 year/6 monthly	Sr CEA, Sr CA 19–9, clinical examination
4/5 year/yearly	Sr CEA, Sr CA 19–9, clinical examination

CECT (Thorax+abdomen+pelvis): Every 6 months for 2 years then every 12 months thereafter till 5 years.

PETCT: Not recommended.

Colonoscopy: Every 1 year after surgery and every 5 years thereafter. If presurgery colonoscopy is incomplete due to obstruction then should be done at 6-months post-surgery.

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Pancreatic Cancer

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Abbreviations

BRPC	Borderline resectable pancreatic cancer
DWI	Diffusion-weighted imaging
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasonography
IPMN	Intraductal papillary mucinous neoplasm of the pancreas
MCN	Mucinous cystic neoplasm
MDCT	Multi-detector computed tomography
MRCP	Magnetic resonance cholangiopancreatography
NCCN	National Comprehensive Cancer Network
PV	Portal vein
SBRT	Stereotactic body radiation therapy
SMV	Superior mesenteric vein

1 Introduction

Pancreatic cancer has a dismal prognosis with incidence and the mortality curves running parallelly [1]. Despite treatment advances, 5-year survival across all stages remains as low as 6–7%. This is attributable to many factors but perhaps the most important reason is the late diagnosis in advanced stage. Most patients remain asymptomatic until the disease progresses to an advanced stage and only 20% of patients are eligible for resection at presentation [2]. Despite curative resection, the reported 5-year survival rate for resected cases remains low up to 25% [1]. This aggressive tumor biology leads to early recurrence and metastasis. In this review, we discuss epidemiology, risk factors, diagnosis, and management of pancreatic cancer.

2 Epidemiology: Indian and Global Scenario

Pancreatic cancer is the 13th most common cancer in the world and eighth most common cause of cancer-related deaths amounting to about 200,000 deaths per year worldwide [3]. Incidence in Europe and USA is also rising with pancreatic cancer being projected to be the second leading cause of cancer deaths in USA by 2030 [3]. The incidence of pancreas cancer is lower in Indian, African, and southeast Asian population; however, these estimates are marred by under-reporting. In the Indian context, the reported incidence is 0.5–2.4 per 100,000 men and 0.2–1.8 per 100,000 women [4, 5].

Pancreatic cancer is predominantly a disease of elderly commonly seen among patients between 60 and 80 years of age [6]. Indian population seem to be affected by the disease earlier with a younger median age of presentation (52–55 years) [7, 8]. It is also seen more commonly in men as compared to women with a male to female ratio of 1.5:1 [5].

3 Risk Factors

Cigarette smoking is the most common and well-documented risk factor for developing pancreas cancer. Even after cessation for at least 10 years, there is 75% increased risk as compared with general population [9]. Chronic pancreatitis is another factor associated with raised lifetime risk of pancreatic cancer [10]. Diabetes is not merely a marker of pancreatic dysfunction as a result of neoplasia but a risk factor for cancer as diabetic patients have an additional 30% risk of pancreatic cancer that persists for more than 20 years after initial diagnosis of diabetes [11]. Advancing age is strongly associated

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Table 1 Inherited disorders with increased risk of pancreatic ductal adenocarcinoma

Familial breast and ovarian cancer, *BRCA2*
Familial atypical multiple mole melanoma syndrome,*CDKN2A* (*P16*)
Peutz-Jeghers syndrome, *STK11* (*LKB1*)
Hereditary pancreatitis, *PRSS1*; *SPINK1*
Hereditary non-polyposis colorectal cancer (Lynch syndrome)
Familial pancreatic cancer, *PALB2*
Ataxia-telangiectasia (biallelic), *ATM* 11

with pancreatic cancer with 20 times higher risk for individuals older than 50 years as compared to younger persons and the median age at presentation being 71 years. Though alcohol is a risk factor for developing pancreatitis, studies have failed to show its association with pancreatic cancer [12, 13]. Similarly, although 10% cases of pancreatic cancer are familial, the genetic basis for most remains unknown. Several genetic syndromes have been associated with pancreatic cancer, but these account for a few cases of familial pancreatic cancer (Table 1) [14–16]. Obesity, specifically high body-mass index (BMI) and centralized fat distribution is also known to increase the risk for pancreas cancer [17].

4 Clinical Presentation

In early stage of the disease, usually patients are asymptomatic. With advancing stage, patients start manifesting symptoms, and the most common presenting symptoms are pain, jaundice, and weight loss. A large case-control study that compared the incidence of early pancreatic cancer symptoms reported 12 alarm symptoms for pancreatic cancer: weight loss, abdominal pain, nausea and vomiting, bloating, dyspepsia, new-onset diabetes, changes in bowel habit, pruritus, lethargy, back pain, shoulder pain, and jaundice [18]. Back pain, lethargy, and new-onset diabetes are unique features of pancreatic cancer. Unexplained superficial thrombophlebitis that may sometimes migrate (classic Trousseau syndrome) is also reported with pancreatic cancer, and it reflects the hyper-coagulable state associated with pancreatic cancer [19]. Some patients develop skin manifestations which are paraneoplastic phenomena.

Tumor location within the organ impacts the initial presentation. Approximately 60–70% of exocrine pancreatic cancers are located in the head of the pancreas, while 20–25% are in the body/tail [20]. Head tumors often present with jaundice, steatorrhea, and weight loss while body and tail cancers more commonly have backache and abdominal pain [21]. Metastatic disease can also manifest as presenting symptoms. Metastasis commonly occurs in liver, peritoneum, lungs, and, less frequently, bones with presentation varying as per organ involved. The presence of an abdominal mass, ascites, left supraclavicular lymphadenopathy (Virchow's node), palpable periumbilical mass (Sister Mary Joseph's node), or a palpable rectal shelf suggests advanced incurable cancer.

5 Evaluation and Work-Up

The diagnostic evaluation for these patients includes serologic evaluation and abdominal imaging. Further testing is based upon the findings of the initial tests and clinical presentation and risk factors. Patients with jaundice or epigastric pain should have an assay of serum aminotransferases, alkaline phosphatase, and bilirubin to determine if cholestasis is present. In addition, patients with epigastric pain and a history suggestive of acute pancreatitis should also be evaluated with a serum amylase and lipase.

5.1 Tumor Markers

Out of many serum markers for pancreatic cancer, the most useful is carbohydrate antigen 19-9 (CA 19-9) with sensitivity and specificity rates ranging from 70% to 92%, and 68% to 92%, respectively. CA 19-9 levels at initial presentation and in the postoperative setting serve as prognostic markers and as an indicator of disease activity in patients with initially elevated levels [22, 23]. In patients with potentially resectable pancreatic cancer, the preoperative CA 19-9 level also helps in prediction of radiographically occult metastatic disease leading to better selection of cases for staging laparoscopy in order to avoid futile laparotomies. In addition, serial monitoring of CA 19-9 levels (once every one to three months) is useful in postoperative surveillance and to determine serologic response in those receiving chemotherapy for advanced disease. The rise in CA 19-9 levels is usually observed before the recurrent disease is appreciated on imaging [22, 23].

5.2 Imaging Modalities

5.2.1 Transabdominal Ultrasonography

Owing to operator dependence and patient's factors like obesity and bowel gas hampering visualization of pancreas, the sensitivity and specificity of transabdominal ultrasound for pancreatic cancer remain low varying from 75% to 89% and from 90% to 99%, respectively [24].

5.2.2 CT Scan

Contrast enhanced multi-detector computed tomography (MDCT) is useful for the diagnosis of suspicious pancreatic lesions, assessment of resectability and vascular invasion as well as diagnosis of metastatic lesions and has become the imaging modality of choice [25].

Characteristic CT findings diagnostic for pancreas cancer [26]:

- Hypo-attenuation (sensitivity 75% and specificity 84%)
- Ductal dilatation (50% and 78%)

- Ductal interruption (45% and 82%)
- Distal pancreatic atrophy (45% and 96%)
- Pancreatic contour anomalies (15% and 92%)
- Common bile duct dilation (5% and 92%)

Comprehensive imaging of a suspected pancreatic cancer patient includes several dynamic phases of contrast injection termed as "pancreas protocol" CT scan.

It consists of the following phases:

- The arterial phase of enhancement: Includes first 30 seconds after the start of the contrast injection, yielding excellent opacification of the celiac axis, superior mesenteric artery (SMA), and peripancreatic arteries.
- •Pancreatic phase: A period of 40–50 seconds after contrast injection having best attenuation difference between the tumor and normal pancreas, which increases the lesion conspicuity. This is best achieved after peak enhancement of the aorta in the arterial phase but before peak enhancement of the liver, which occurs in the portal venous phase.
- The venous phase: Taken at 60–70 seconds after the start of the contrast injection, the venous phase yields superior enhancement of the superior mesenteric, splenic, and portal veins. Additionally, it also gives peak hepatic enhancement optimizing the detection of hepatic metastases.

Overall accuracy of MDCT for diagnosis is about 90%. The accuracy of MDCT to define resectability is 85–95% [27, 28].

5.2.3 MRI

The sensitivity (83–85%) and specificity (63%) of gadolinium-enhanced MRI are similar to that of MDCT [29]. Diffusion-weighted imaging (DWI) is an MRI technique utilizing the Brownian motion of water molecules in tissue [30]. MRI-DWI could be preferred to CT as it facilitates precise depiction of pancreatic lesions without radiation exposure. Magnetic resonance cholangiopancreatography (MRCP) allows the noninvasive picturisation of the pancreatic duct and biliary tract. It is particularly useful for diagnosis of small pancreatic masses and has almost replaced invasive endoscopic retrograde cholangiopancreatography (ERCP) for this purpose. However, it does not permit tissue sampling [31]. It is also useful in intraductal papillary mucinous neoplasm of the pancreas (IPMN) and in chronic pancreatitis, both of which may be associated with pancreatic cancer.

5.2.4 PET

FDG-PET plus CT is not clearly shown to have an advantage for diagnosing pancreatic cancer compared with contrast enhanced MDCT [32]. False negative results in hyperglycemia and possible false positive results in inflammatory masses caused by pancreatitis limit the use of this modality.

5.3 Endoscopic Techniques

5.3.1 ERCP

Brushing cytology and aspiration cytology using an endoscopic naso-pancreatic catheter placed during ERCP are reported to improve the diagnostic accuracy in pancreatic cancers [33, 34]. Moreover, probe-based confocal laser endomicroscopy is highly sensitive to diagnose cancer in pancreaticobiliary strictures [35]. However, with availability of MDCT and dynamic contrast MRI, ERCP for diagnosis has almost become obsolete. ERCP definitely has a therapeutic role in pancreatic head cancers with biliary obstruction and a very high jaundice (>15 mg/dL) or symptomatic jaundice (fever, features of cholangitis). After stenting, it is prudent to delay the surgery (pancreaticoduodenectomy) for 4–6 weeks in order to minimize infections complications and improve postoperative outcomes [36].

5.3.2 Endoscopic Ultrasonography

Endoscopic ultrasonography (EUS) has high sensitivity and specificity to detect pancreatic cancer. EUS-guided fine-needle aspiration has accuracy of more than 85–90% for pancreatic cancer.

In summary, MDCT with angiography or MRI/MRCP should be the first imaging modality in a patient suspected with pancreatic cancer. EUS is recommended to assess highly suspicious lesions which are not clearly demonstrated on CT/MRI and in borderline resectable tumors for assessment of vascular involvement. It also helps in obtaining a tissue diagnosis. Role of PET-CT is limited to ruling out distant metastasis in locally advanced lesions [37].

5.4 Pathology

5.4.1 Histopathology

Pancreatic ductal adenocarcinoma is the commonest pancreatic neoplasm which is invasive mucin-producing gland-forming tumor. A strong stromal desmoplastic reaction is commonly seen in surrounding region. Most pancreatic adenocarcinomas arise from noninvasive precursor lesions known as pancreatic intraepithelial neoplasms [38]. Few of them have cystic precursors—namely, IPMNs and mucinous cystic neoplasms (MCNs).

Pancreatic adenocarcinoma is divided into three grades (well, moderately, and poorly differentiated) depending upon the degree of differentiation. Several key features must be documented in the histopathology report while analyzing any pancreatic resection specimen for pancreatic cancer. Tumor size and invasion into surrounding structures have to be carefully assessed for accurate determination of the T stage. It has been recommended that at least 15 nodes are required for accurate N staging [39]. All margins, including the proximal (gastric or duodenal), distal (duodenal), uncinate, bile duct, and pancreatic resection margins should be checked for presence of invasive carcinoma component. A standardized protocol pancreaticoduodenectomy specimen evaluation involving margin staining, axial slicing, and tissue sampling has been proven to influence reporting of resection margins [40, 41].

5.4.2 Molecular Pathology

Four major driver genes have been described for pancreatic ductal adenocarcinoma (one oncogene and three tumor suppressor genes) [42–44].

- KRAS: Encodes a small GTPase mediating downstream signaling from growth factor receptors and is the commonest oncogene involved. Somatic mutations in KRAS gene are seen in more than 90% of tumors.
- CDKN2A: Most frequently altered tumor suppressor gene with loss of function in more than 90% of ductal adenocarcinomas, it encodes a protein essential for cell-cycle regulation.
- TP53: A tumor suppressor gene plays a key role in the cellular stress response and is mutated in a wide range of tumor types.
- SMAD4: This tumor suppressor gene mediates signal pathway downstream of the transforming growth factor β (TGFβ) receptor and its inactivation is seen in about 50% of pancreatic ductal adenocarcinomas.

Recent studies have identified alterations in hundreds of other genes in carcinogenesis of pancreatic adenocarcinoma. However, it is difficult to differentiate driver genes that causally contribute to development of cancer from the passenger genes which aggregate random mutations during cell division.

5.5 Referrals Including Genetic Counseling

Familial predisposition is seen in approximately 10% of pancreatic cancers. The exact genetic basis for this predilection is unknown in most cases, and 80% of patients with a family history of pancreatic cancer do not have any known genetic cause [11]. Patients with suspected hereditary cancer syndrome should be considered for genetic counseling [45]. A thorough family history specifically of pancreatitis, melanoma, and cancers of the pancreas, colon/rectum, breast, and ovaries should be noted. Family history of cancer, young age, as well as Ashkenazi Jewish ancestry should lead to a referral for genetic counseling. At-risk family members should also be offered genetic counseling. Patients with a significant family history should be advised on risk-modifying strategies like smoking cessation and weight loss.

6 Principles of Management

Treatment of pancreatic cancer varies according to the stage with a multimodality and multidisciplinary approach that includes surgery, chemotherapy, and radiation therapy as well as symptom relief and palliative care. Baseline performance status, comorbidities, and goals of care must be taken into consideration before planning the treatment.

During the evaluation process, nonmetastatic patients are categorized into resectable, borderline resectable, or unresectable tumors [46] (see Fig. 1a–c).

Primary surgical resection should only be offered to patients with resectable tumors with good performance status and a favorable comorbidity profile appropriate for a major abdominal operation. Following resection, all patients are offered adjuvant chemotherapy. Patients who undergo R1 resection are considered for additional adjuvant radiotherapy.

Tumors with venous involvement of the superior mesenteric vein or portal vein, gastroduodenal artery encasement up to the hepatic artery, and abutment of the superior mesenteric artery of ≤180° are considered as “borderline resectable.” The risk for incomplete (R1) resection with upfront surgery in these cases is high and hence, downstaging with neoadjuvant chemotherapy or chemoradiotherapy and reassessment for curative resection is the preferred approach.

Tumors with >180° encasement of superior mesenteric artery, celiac axis, non-reconstructable superior mesenteric vein involvement or superior mesenteric-portal vein confluence occlusion, or direct infiltration of the inferior vena cava and aorta are considered unresectable cancers. These patients are managed initially with chemotherapy with or without radiotherapy. A small fraction of these tumors may respond well enough to chemotherapy and/or radiotherapy to warrant consideration for surgical resection (conversion chemotherapy).

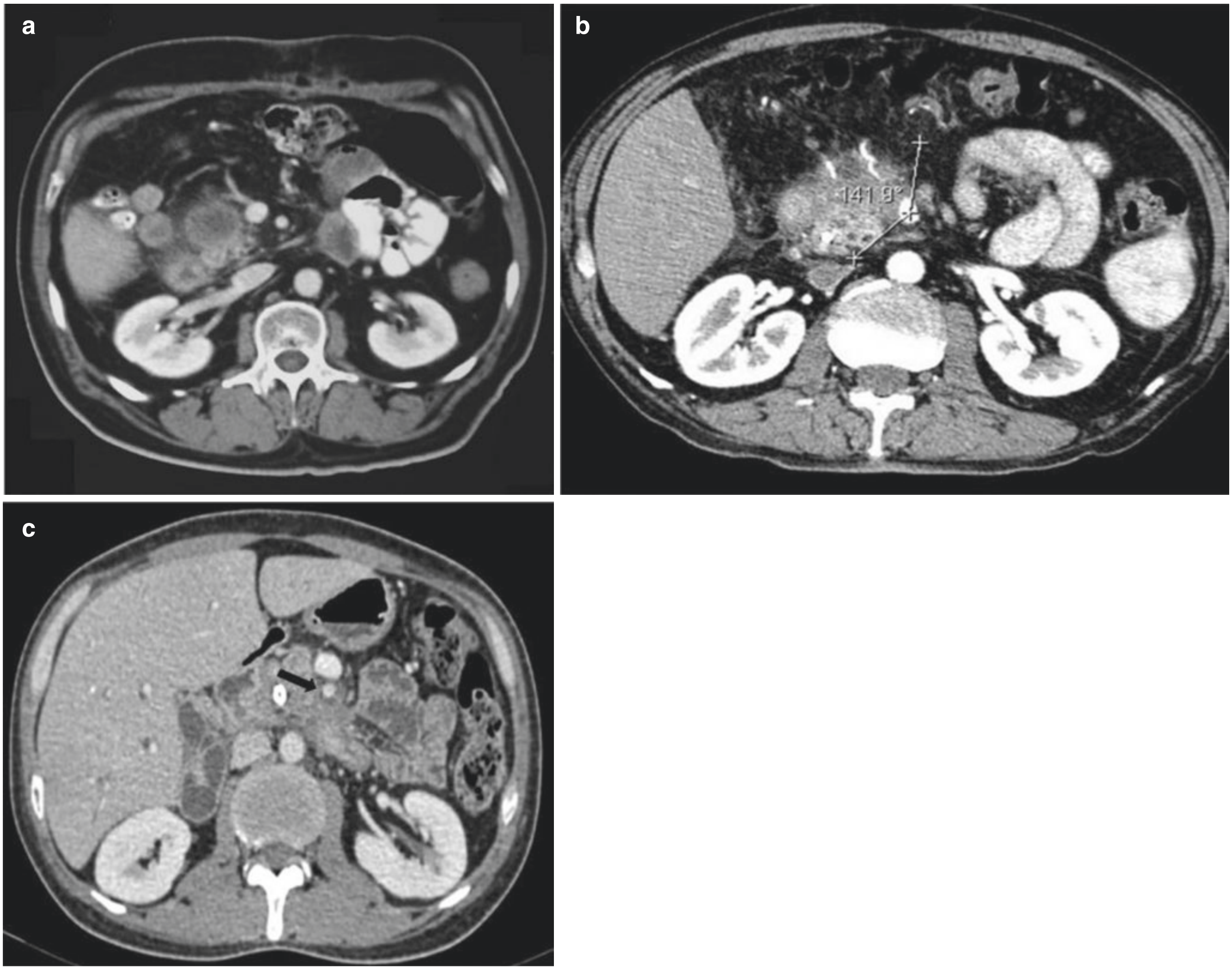


Fig. 1 (**a**) Resectable pancreatic cancer without involvement of surrounding vasculature. (**b**) Borderline resectable pancreatic cancer complete involvement with non-visualization of SMV/PV and SMA involvement of <180°. (**c**) Locally advanced pancreatic cancer with encasement of superior mesenteric artery >180°

7 Surgical Management

7.1 Indication for Surgery

Regarded as the only available treatment option with potential for achieving cure, surgical resection results in significantly longer survival compared with any other treatment options. Superior mesenteric vein (SMV) and portal vein (PV) involvement was considered to be unresectable in the past. However, curative surgery including SMV/PV resection and vascular reconstruction has become standard of care in specialized high-volume centers.

Nonmetastatic pancreatic cancer can be divided into three categories:

1. Resectable
2. Borderline resectable
3. Locally advanced

National Comprehensive Cancer Network (NCCN) guidelines outline various radiological characteristics to define these categories [47] (Table 2).

However, the definitions of these three categories are not uniform as resectability varies based upon surgical experience and techniques. For example, one of the most commonly used definitions of borderline resectable pancreatic cancer (BRPC) includes nonmetastatic ca pancreas cases with venous involvement of the superior mesenteric vein or portal vein or gastroduodenal artery encasement up to the hepatic artery and/or tumor abutment of the superior mesenteric artery of less than or equal to 180°. In specialized centers, en bloc resection of the portal vein or superior mesenteric vein, or both, is commonly and safely practiced in the setting of borderline resectable tumors involving these veins [48]. However, abutment of a major artery such as the superior mesenteric artery often results in positive surgical margin

Table 2 Outcomes following >2100 Whipple resections, Tata Memorial Hospital (unpublished data)

Period*	A (1992–2001)	B (2003–July 2009)	C (Aug 2009–Dec 2011)	D (Jan 2012–Dec 2023)	Total
N	144	206	150	1658	**2158**
Resections/year	16	34	60	150	
Median age	50	53 (18–74)	53 (8–82)	56 (6-86)	**53 (6–85)**
POPF[a]	16% (23)	8% (16)	10.7% (16)	16.5% (274)	**15.24% (329)**
Bile leaks	6.3% (9)	3.4% (7)	0.7% (1)	1.01% (16)	**1.52% (33)**
DGE[b]	6.9% (10)	2.4% (3)	2% (3)	11.2% (185)	**9.3% (201)**
PPH[c]	11.1% (16)	5% (10)	2% (3)	3.6% (61)	**4.17% (90)**
Median hospital stay	16	15	12	12	**12**
Morbidity	41.7% (60)	30% (61)	29% (44)	30.69% (509)	**31.2% (674)**
Mortality	6.3% (9)	4.8% (10)	5.3% (8)	3.31% (55)	**3.7% (82)**

[a] *POPF* post operative pancreatic fistula
[b] *DGE* delayed gastric emptying
[c] *PPH* post pancreatectomy hemorrhage
(a, b & c, as per ISGPS definition)
***Period**: Period A: Routine use of preoperative biliary drainage, Period B: Standardization of pancreatic resections and anastomosis, Period C: Increasing volumes and refinement of surgical technique, Period D: Further increase in volumes, extended/vascular resection, use of neo-adjuvant Rx

after surgical resection and is presently not recommended [48–50].

The decision about surgical resection, however, should not be based on anatomic criteria alone. The biological behavior of the cancer and the patient's reserves to cope up with the physiological strain of a demanding surgery must be taken into consideration in the decision-making process. The recent International consensus on definition and criteria of BRPC has defined BRPC according to three distinct dimensions [51], viz. anatomical (A), biological (B), conditional (C):

- The anatomical criteria of BRPC: A tumor that is at high risk for margin positive resection (R1 or R2).
- The biological criteria of BRPC: Findings that raise the possibility (but not certainty) of extra-pancreatic metastatic disease (high serum CA 19-9 levels / radiologically suspected but unproven metastases).
- The conditional criteria of BRPC: High risk for morbidity or mortality post-surgery because of host-related factors including performance status and comorbidities.

These refinements should ensure standard reporting of outcomes ultimately resulting in establishment of the best possible management approach including use of neoadjuvant therapies for this unique subset of pancreatic cancers.

7.2 Surgical Techniques and Other Considerations

Surgical treatment for pancreatic cancer requires different procedures like pancreaticoduodenectomy, distal pancreatectomy with splenectomy, and total pancreatectomy depending on the site of tumor and extent of involvement of pancreas. Standard lymphadenectomy for pancreatoduodenectomy includes removal of lymph node stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b [52]. After pancreaticoduodenectomy, pancreatic, biliary and gastric reconstruction is performed. Clinically relevant postoperative pancreatic fistula (CR-POPF) is the most troublesome complication after pancreatoduodenectomy. There has been a lot of debate regarding the technique used to do pancreatico-enteric anastomosis and development of CR-POPF. The most commonly used techniques include pancreaticojejunostomy (Fig. 3) and pancreaticogastrostomy [53]. Superiority of one of these techniques over another has not been proven and neither completely eliminate development of CR-POPF.

Survival advantage of extended resections including wide resections of the para-aortic lymph nodes and nerve plexus, and multi-visceral resections is not backed up by high level of evidence and hence these procedures are not recommended routinely [54–56]. These extended resections may lead to compromised quality of life like intractable diarrhea. However, in highly selected patients, with preserved performance status and stable or non-progressive disease on neoadjuvant treatment, extended resection can provide survival benefit over palliative care [57]. Radical surgery in presence of oligo-metastatic disease has also been reported with reported survival advantage in highly selected patients [58].

SMA first approach (six different approaches, Fig. 2) was proposed as a new modification of standard pancreaticoduodenectomy for improvement in margin positivity in borderline resectable pancreatic cancer [59]. A systematic review reported that the SMA first approach is associated with decreased blood loss, transfusion requirement, pancreatic

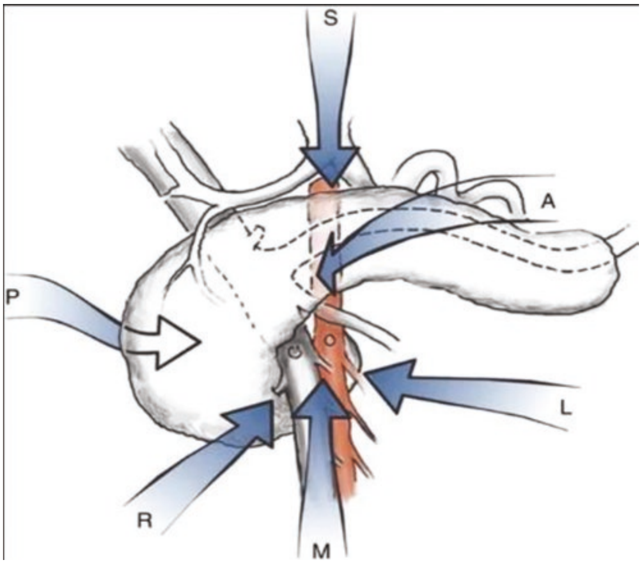


Fig. 2 Diagram showing six approaches to the superior mesenteric artery: *S* superior approach, *A* anterior approach, *P* posterior approach, *L* left posterior approach, *R* right/medial uncinate approach, *M* mesenteric approach

fistula rates, delayed gastric emptying, and lower local and metastatic recurrence rate [60, 61].

Laparoscopic approach in pancreatic cancer surgery is getting popular. Retrospective cohort studies have shown that laparoscopic distal pancreatectomy for cancer is non-inferior to open surgery in the context of overall survival. It is also beneficial to patients with an earlier return to diet and a shorter hospital stay [62]. The results from the recent LEOPARD-1 trial also show decreased recovery time without increasing overall complication rates and establish minimally invasive resection for body and tail of pancreas lesions as a preferable option [63]. By contrast, laparoscopic pancreaticoduodenectomy is complex and needs highly trained surgical skills. The generalized application of this technique remains questionable as seen with high morbidity and subsequent premature termination of LEOPARD-2 trial [64–66].

Hospital volume is arguably an important factor affecting mortality, complications, length of hospital stay, margin status, survival, and overall cost after pancreaticoduodenectomy [53, 67–69]. The complications and mortality largely depend on pancreatic anastomotic leak. Consistent practice of any standardized technique of anastomosis by an experienced surgeon helps in decreasing the rate of clinically relevant postoperative pancreatic fistula [53, 70]. Results of >2100 pancreaticoduodenectomies from Tata Memorial Hospital [71] also indicate the same (see Table 2). Therefore, it is recommended that pancreaticoduodenectomy should be done in specialized centers with experienced teams performing a large number (>15–20) of pancreatic resections per year [50].

8 Medical Management

8.1 Adjuvant Chemotherapy for Resected Pancreatic Cancer

The 5-year survival of pancreatic cancer patients undergoing surgery alone is 10-15% with median overall survival being 11-20 months. This has improved significantly with the use of adjuvant chemotherapy and has become standard of care. The results of ESPAC-01 trial showed that adjuvant chemotherapy with folinic acid (leucovorin) and fluorouracil was associated with better survival in patients with resected pancreatic cancer as compared with chemotherapy alone [72]. Another randomized trial, CONKO-001, comparing six cycles of adjuvant gemcitabine versus no adjuvant treatment after surgery found increased disease-free survival and overall survival in gemcitabine arm [73]. Further, ESPAC-04 trial which was a phase III randomized control trial comparing adjuvant gemcitabine versus combination of gemcitabine with capecitabine established combinational use as the superior regime for adjuvant therapy [74]. The recent PRIODIGE-24 trial showed a much superior median survival of 54.4 months with adjuvant modified FOLFIRINOX regimen as compared to 35 months with gemcitabine alone. The 3-year survival of 63.4% was seen in mFOLFIRINOX arm. The results of PRODIGE-24 made mFOLFRINOX the chemotherapy regimen of choice in patients with good performance status [75].

8.2 Neoadjuvant Chemotherapy/Radiotherapy

The role of neoadjuvant therapy has been investigated in many clinical trials in the USA, Europe, and Japan in order to achieve better local control and, ultimately, to improve survival of patients. Another important rationale for neoadjuvant therapy is better selection of patients who do not have the complications of aggressive disease or latent metastasis. Full-dose chemotherapy is better tolerated before surgery and preoperative therapy may be more effective than postoperative therapy because the resected tumor bed is associated with poor drug delivery and low sensitivity to chemotherapy and radiation due to poorly oxygenated tissues [76]. R0 resection rates are higher in BRPC after neoadjuvant therapy and survival of patients who undergo surgical resection is better than that of those who do not. Few small RCTs have shown benefit of neoadjuvant therapy in BRPC. A Korean phase II/III RCT by Jang et al. comparing neoadjuvant chemoradiation to upfront surgery in patients with BRPC. The intention-to-treat analysis of this study showed that the 2-year survival rate and median survival (40.7% and 21 months vs. 26.1% and 12 months) (hazard ratio 1.495, 95% CI [0.66, 3.36];

$p = 0.028$) were significantly better for patients with neoadjuvant therapy [77]. Recently published PREOPANC trial demonstrated significantly better overall survival in patients receiving gemcitabine-based chemoradiation as compared to upfront surgery group (35.2 months vs 19.8 months). The benefit was statistically significant in BRPC patients [78]. ALLIACE A21501 trial, a phase II trial evaluating mFOLFIRINOX in neoadjuvant setting showed median overall survival of 31 months with neoadjuvant therapy with no benefit of additional radiation. The results of this trial with extrapolation from experience of FOLFIRINOX has lead this regimen to be the most commonly used and effective chemotherapy regimen in neoadjuvant approach [79].

Neoadjuvant therapy is becoming increasingly popular due to high response rates and high R0 resection rates, and there is some evidence to recommend neoadjuvant therapies against upfront surgical resection in patients with BRPC. However, utility of neoadjuvant therapy in resectable pancreatic cancer continues to be a debated unanswered question [80]. Most of the clinical trials are limited due to lack of accrual, probably due to fear of loss of the opportunity of surgical resection [81].

8.3 First-Line Chemotherapy for Metastatic Pancreatic Cancer

Chemotherapy is the main line of treatment for metastatic pancreatic cancer. In a landmark clinical trial published in 1997, that compared gemcitabine and fluorouracil, median survival of 4.41 months and 5.65 months was seen in the fluorouracil group and gemcitabine group, respectively [82]. Since then, gemcitabine has been accepted as the standard chemotherapy.

In the phase 3 ACCORD-11 trial, the FOLFIRINOX regimen (oxaliplatin 85 mg/m^2, folinic acid [leucovorin] 400 mg/m^2, irinotecan 180 mg/m^2, bolus fluorouracil 400 mg/m^2, infusional fluorouracil 2400 mg/m^2 over 46 h, every 14 days) was shown to have better response, progression-free survival, and overall survival compared to gemcitabine for metastatic pancreatic cancer [83]. Although this is an attractive benefit, it has to be noted that FOLFIRINOX was associated with higher risk of febrile neutropenia, sensory neuropathy, and gastrointestinal toxicities. Hence, this regimen is recommended only for patients aged 75 years or younger with good performance status and without significant risk of cholestasis or cholangitis.

The MPACT trial, a phase III trial, showed that gemcitabine plus nanoparticle albumin bound paclitaxel (nab-paclitaxel) showed superior overall survival and progression-free survival to gemcitabine alone in metastatic pancreatic cancer patients [84]. The adverse effects of this regimen seem to be less severe than FOLFIRINOX. It can be used in a wider range of patients.

Finally, on the basis of current evidence, both FOLFIRINOX and gemcitabine plus nab-paclitaxel are the current regimens of choice for patients with good performance status. Gemcitabine plus erlotinib may be another option for patients who develop skin rash. Gemcitabine monotherapy should be used in patients with compromised performance status.

8.4 Second-Line Chemotherapy for Metastatic Pancreatic Cancer

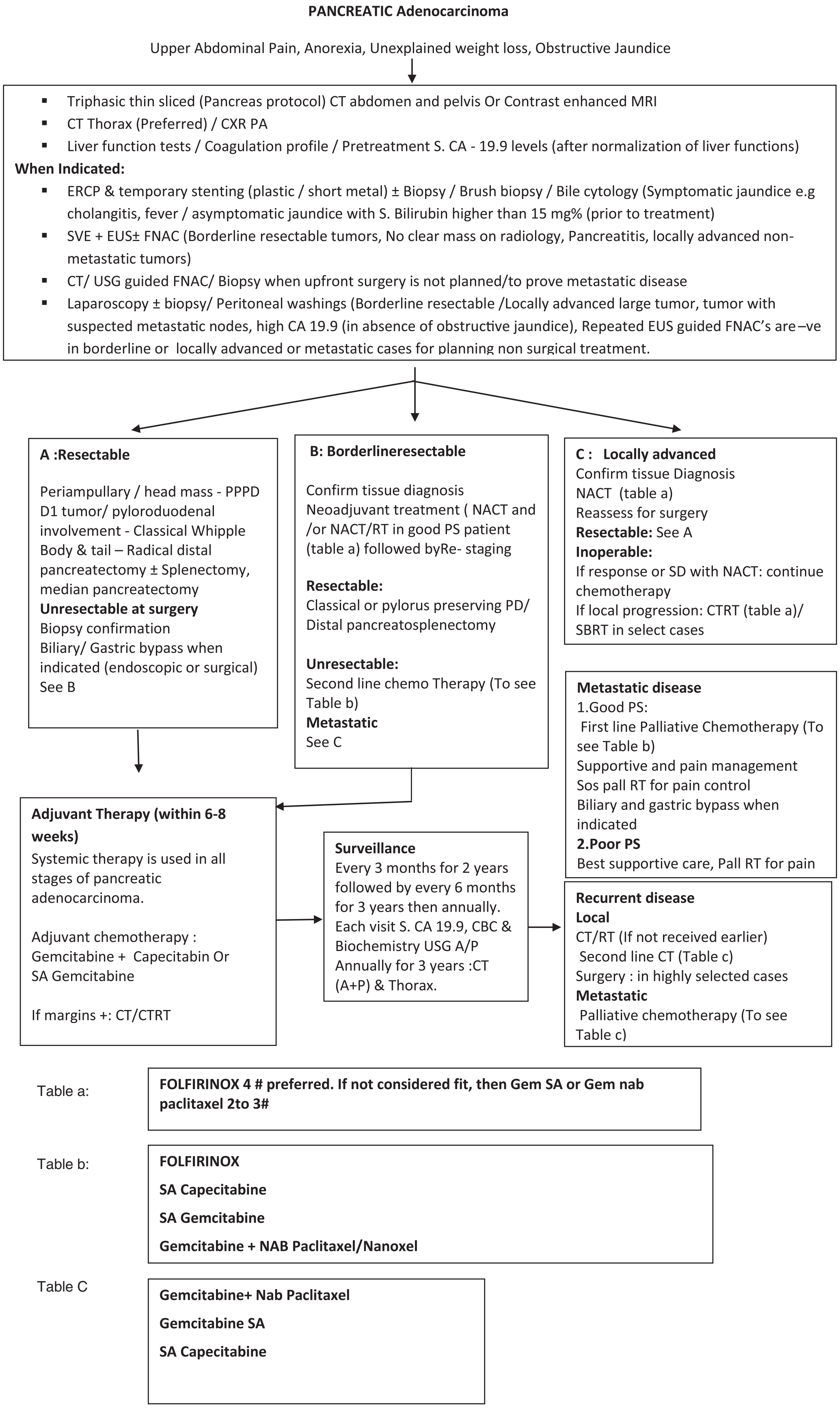
After progression with first-line chemotherapy, second-line chemotherapy should be considered in patients with good performance status as there is some benefit [85], although there is no established evidence regarding the regimen of second-line chemotherapy.

9 Radiotherapy

Radiotherapy is used with chemotherapy for pancreatic cancer in adjuvant or definitive settings, or as neoadjuvant approach as discussed in the previous section.

There have been increasing reports showing improvement in margin negative R0 resections with neoadjuvant approach using chemoradiation [86]. Stereotactic body radiation therapy (SBRT) and intensity-modulated radiation therapy (IMRT) are proven to be safe and effective in neoadjuvant [87] and palliative settings.

The role of definitive chemoradiation therapy for locally advanced pancreatic cancer has been intensively studied. However, the survival benefits of chemoradiation therapy remain a hotly debated topic [88]. The ECOG 4201 trial compared chemoradiotherapy with chemotherapy in patients with locally advanced pancreatic cancer. The median survival was 9.2 months for chemotherapy in gemcitabine arm compared to 11.1 months in chemoradiotherapy arm. However, due to small number of recruited patients, the study could not reach any definitive conclusions [89]. A randomized study comparing chemoradiation therapy and chemotherapy after 4 months of gemcitabine with or without erlotinib (LAP 07) showed chemoradiation was not superior to chemotherapy locally advanced pancreatic cancer [90]. Further studies are required to establish the potential survival advantages of chemoradiation therapy in these locally advanced tumors. A management algorithm for pancreatic adenocarcinoma is presented in Fig. 3.



PANCREATIC Adenocarcinoma

Upper Abdominal Pain, Anorexia, Unexplained weight loss, Obstructive Jaundice

- Triphasic thin sliced (Pancreas protocol) CT abdomen and pelvis Or Contrast enhanced MRI
- CT Thorax (Preferred) / CXR PA
- Liver function tests / Coagulation profile / Pretreatment S. CA - 19.9 levels (after normalization of liver functions)

When Indicated:

- ERCP & temporary stenting (plastic / short metal) ± Biopsy / Brush biopsy / Bile cytology (Symptomatic jaundice e.g cholangitis, fever / asymptomatic jaundice with S. Bilirubin higher than 15 mg% (prior to treatment)
- SVE + EUS± FNAC (Borderline resectable tumors, No clear mass on radiology, Pancreatitis, locally advanced non-metastatic tumors)
- CT/ USG guided FNAC/ Biopsy when upfront surgery is not planned/to prove metastatic disease
- Laparoscopy ± biopsy/ Peritoneal washings (Borderline resectable /Locally advanced large tumor, tumor with suspected metastatic nodes, high CA 19.9 (in absence of obstructive jaundice), Repeated EUS guided FNAC's are –ve in borderline or locally advanced or metastatic cases for planning non surgical treatment.

A :Resectable

Periampullary / head mass - PPPD
D1 tumor/ pyloroduodenal involvement - Classical Whipple
Body & tail – Radical distal pancreatectomy ± Splenectomy, median pancreatectomy
Unresectable at surgery
Biopsy confirmation
Biliary/ Gastric bypass when indicated (endoscopic or surgical)
See B

B: Borderlineresectable

Confirm tissue diagnosis
Neoadjuvant treatment (NACT and /or NACT/RT in good PS patient (table a) followed byRe- staging

Resectable:
Classical or pylorus preserving PD/ Distal pancreatosplenectomy

Unresectable:
Second line chemo Therapy (To see Table b)
Metastatic
See C

C : Locally advanced
Confirm tissue Diagnosis
NACT (table a)
Reassess for surgery
Resectable: See A
Inoperable:
If response or SD with NACT: continue chemotherapy
If local progression: CTRT (table a)/ SBRT in select cases

Metastatic disease
1.Good PS:
First line Palliative Chemotherapy (To see Table b)
Supportive and pain management
Sos pall RT for pain control
Biliary and gastric bypass when indicated
2.Poor PS
Best supportive care, Pall RT for pain

Adjuvant Therapy (within 6-8 weeks)
Systemic therapy is used in all stages of pancreatic adenocarcinoma.

Adjuvant chemotherapy :
Gemcitabine + Capecitabin Or
SA Gemcitabine

If margins +: CT/CTRT

Surveillance
Every 3 months for 2 years followed by every 6 months for 3 years then annually.
Each visit S. CA 19.9, CBC & Biochemistry USG A/P
Annually for 3 years :CT (A+P) & Thorax.

Recurrent disease
Local
CT/RT (If not received earlier)
Second line CT (Table c)
Surgery : in highly selected cases
Metastatic
Palliative chemotherapy (To see Table c)

Table a:

FOLFIRINOX 4 # preferred. If not considered fit, then Gem SA or Gem nab paclitaxel 2to 3#

Table b:

FOLFIRINOX
SA Capecitabine
SA Gemcitabine
Gemcitabine + NAB Paclitaxel/Nanoxel

Table C

Gemcitabine+ Nab Paclitaxel
Gemcitabine SA
SA Capecitabine

Fig. 3 Management algorithm

10 Prognosis

As discussed above, majority of patients with pancreatic cancer die of their disease, even after complete resection. The most important prognostic factor for patients undergoing R0 resection is nodal status. Five-year survival after surgery is approximately 10% for node-positive disease [91], while it is approximately 30% for node-negative disease [92]. In addition to stage, the status of the surgical margins (involved or uninvolved), tumor differentiation, presence or absence of lymphatic and peri-neural invasion, and both preoperative and postoperative serum CA 19-9 levels are important factors affecting survival in pancreatic ductal adenocarcinoma [93–95]. The median overall survival for untreated, locally advanced, unresectable pancreatic cancer is 8–12 months which decreases to only 3–6 months for metastatic cancer at presentation. In these patients, current chemotherapy regimens with FOLFIRINOX, the median survival has been shown to be extended in the range of 15–18 months in advanced disease [96].

11 Palliative Management in Advanced Metastatic Disease

Palliative care is equally important as other therapies, and pancreatic cancer patients will require some form of palliation at some point in disease course. These patients usually develop obstructive jaundice and gastric outlet obstruction requiring surgical, endoscopic, or radiological interventions. Technologic improvements have led to replacement of percutaneous biliary drainage by endoscopic stenting in most cases. Large diameter metal stents are preferred over small caliber plastic stents because of the longer patency time and lower incidence of cholangitis [97]. Surgical gastrojejunostomy and endoscopic duodenal stents are feasible options for palliation of gastric outlet obstruction. Endoluminal duodenal stents are especially preferred when life expectancy is limited or in patients with poor performance status.

Pain is a significant debilitating feature of advanced pancreatic cancer, and all patients should receive assessment for the level of pain and degree of pain relief from analgesics at every clinic visit. The backbone of pain management is typically opioid medication, and pain relief is often successfully achieved by opioid analgesics alone. Patients with intractable pain refractory to other medication are managed by inhibition of synaptic pathways within the celiac plexus without nerve destruction (i.e., celiac plexus block using a bolus injection of local anesthetic) or chemical destruction using dehydrated alcohol (celiac plexus neurolysis).

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Gastrointestinal Stromal Tumours

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Abbreviations

CECT	Contrast-enhanced computerized tomography
CSS	Carney-Stratakis syndrome
CT	Carney's triad
CT	Computerized tomography
DOG1	Discovered on GIST1
GIST	Gastrointestinal stromal tumours
ICC	Interstitial cells of Cajal
IHC	Immunohistochemistry
IM	Imatinib mesylate
MRI	Magnetic resonance imaging
PDGFRA	Platelet-derived growth factor receptor α
PET	Positron-emission tomography
PFS	Progression-free survival
SDH	Succinate dehydrogenase
SMT	Submucosal tumours

1 Introduction

Gastrointestinal stromal tumours (GIST) are rare mesenchymal tumours of the gastrointestinal tract, though rarely arising from intra-abdominal soft tissues [1]. They are most commonly seen in stomach (60%) and small intestine (30%) and less commonly in the rectum and omentum [2, 3]. GISTs are either derived from or differentiated towards interstitial cells of Cajal (ICC) (which act as the 'pacemaker' cells of the gastrointestinal tract) or their stem cell precursors [4].

GISTs have often been clubbed together with other smooth muscle neoplasms, though the idea that they were a different set of tumours was proposed as early as the 1980s [5]. The discovery of the c-KIT gene (cellular homologue of the oncogene v-KIT) has led to the recognition of GIST as a separate disease entity [6, 7].

2 Global Incidence, Epidemiology, and Clinical Presentation: Global and India

GISTs are rare diseases, but available data does suggest variances in incidence across geographical regions [8]. They are most commonly seen beyond the age of 50 years (median age—63 years), though they are seen across age-groups as well. There is limited data from India with regard to presentation and incidence [9, 10]. GISTs are rare in the paediatric age group, but are noted in the second decade with a female predilection. They almost exclusively arise in the stomach with frequent nodal involvement in this age-group, though nodal involvement is rarely seen in adults GISTs as well [11].

Approximately 18–25% of patients have GIST are incidentally diagnosed. The most common sites include stomach (60%), jejunum and ileum (30%), duodenum (5%), and colon/rectum (4%).The most common symptomatic presentation (75% of patients) is that of a lump or palpable growth [12]. Occasionally, they may present with emergent complications like an obstruction, bleeding, rupture of tumour, or bowel perforation. Due to increased awareness of GIST as an entity, a new subgroup of GISTs called mini-GISTs (measuring between 1 and 2 cm) and micro-GISTs (measuring <1 cm) are now part of the diagnosed disease spectrum [13].

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3 Molecular Basis of GIST

The KIT and platelet-derived growth factor receptor α (PDGFRA) genes are central in understanding the pathogenesis of GIST and its malignant potential [14]. Mutations in the KIT (70%; commonly in exon 11 and less commonly in exon 9) and PDGFRA (10%; exon 18 and exon 14) genes result in constitutive activation and signalling (in the absence of the endogenous ligand) causing a chain of cellular events leading to the advent of GIST [1, 15]. Mutations in the exon 11 themselves are a heterogeneous group, with different mutations having different biological behaviours [16–18]. GISTs with PDGFRA mutations are possibly less aggressive compared to KIT mutant GISTs. Though 10% of all GISTS are KIT and PDGFRA 'wild', next-generation sequencing in this 'wild type' cohort has identified mutations involving succinate dehydrogenase (SDH) as well as BRAF genes [19]. Patients with SDH deficiencies are usually younger with near universal involvement of the stomach as primary site of GIST. The mutations described, besides being central to the etiopathogenesis of GIST have an increasingly important bearing on the treatment modalities used in GIST.

4 Evaluation and Work-Up

GISTs may often be diagnosed incidentally, though a complete diagnostic evaluation is required for confirmation and staging.

4.1 Endoscopy and Endoscopic Ultrasound (EUS)

The initial investigation for small-sized GISTs would be an EUS—FNA/FNB [20]. EUS-FNA is indicated for lesions measuring >1 cm (usually between 1 and 2 cm) that are suspected to be potentially malignant [21]. An endoscopy is preferred for larger tumours in terms of adequate evaluation as well as taking adequate biopsies.

4.2 Radiology and Nuclear Imaging

A contrast-enhanced computerized tomographic (CECT) scan is the imaging modality of choice for accurate detection and staging of a GIST [22]. In uncommon situations such as in the case of anorectal GISTs, a magnetic resonance imaging (MRI) may provide additional information above and beyond a CECT scan.

Positron-emission tomography (PET) provides functional information that may help in staging, especially when combined with morphological information provided by a CT. A PET/CT is valuable especially in differentiating necrotic tissue from viable tissue, recurrent tumour from scar tissue, and in assessing response post-therapy in GISTs [23]. The Choi criteria, which are a combination of tumour density (15% change) and modified tumour size (>10%), are validated criteria for early response evaluation, but is yet to be routinely used. [24].

4.3 Pathology

- Gross pathology: GISTs are usually well-circumscribed or multinodular tumours that may develop in any portion of the gut wall, but most are centred in the submucosa or the muscularis propria. Cut sections identify grey white, solid tumours, with a fleshy appearance and often show haemorrhage, necrosis, or cystic change [25].
- Microscopic features: Gastrointestinal stromal tumours are cellular lesions, with 70% of cases composed of spindle cells, 20% of epithelioid cells, and the remainder having a mixed cellular composition. Tumour size and mitotic count per 50 HPF are regarded as the best predictor of malignant behaviour in GIST. [26].
- Immunohistochemistry (IHC): On IHC, KIT (CD117) expression is a sensitive and specific marker for GIST, with about 95% of GISTs showing a strong and diffuse cytoplasmic staining for KIT, although some tumours, (e.g. epithelioid morphology), can show membranous staining [27]. Although CD117 is a highly sensitive marker of GIST, it can be consistently expressed in many other tumours, e.g. seminomas, mastocytomas, melanomas, clear cell sarcomas, etc. [28]. DOG1 (Discovered on GIST1) is a commonly used IHC marker along with KIT for the diagnosis of GIST [29]. The sensitivity of KIT and DOG1 is individually approximately 95% for the diagnosis of GIST. Approximately, one-third of KIT-negative GIST stain with DOG1, thereby making it a useful adjunct in the diagnosis of GIST [30]. Other IHC markers which stain positively in GIST include CD34, caldesmon, smooth muscle actin, desmin, S-100 protein, and keratin.
- Although GISTs are the most common mesenchymal tumour of the GI tract, the differential diagnosis includes other tumours in this location, including smooth muscle tumours, nerve sheath tumours, fibromatoses, etc.

5 Principles of Management (Overview)

The management of GIST is based on tumour prognosis and staging once the diagnosis is confirmed. A number of prognostic classification systems have developed over the last two decades for GIST [30–33]. Table 1 offers a snapshot of the widely used system as proposed by Miettinen [26, 34]. Comparative studies of these classifications suggest that while all of them distinguished well in terms of high-risk and low-risk tumours, there was significant heterogeneity in the high-risk groups and more importantly, no significant differences in overall survival between the risk groups [35]. These classifications also do not take into cognizance the relevance of KIT mutation status in their risk assessment.

Once the stage is identified, patients in TMH are treated along the algorithm shown in Fig. 1.

Table 1 Rates of progression-free survival for gastrointestinal stromal tumours (GISTs) of stomach, small intestine, and rectum as per Miettinen's classification

Tumour size (cm)	Mitotic rate (HPFs)	Gastric	Jejunum/ileum	Duodenum	Rectum
≤2	≤5/50	100	100	100	100
2–5	≤5/50	98.1	95.7	91.7	91.5
5–10	≤5/50	96.4	76	66	43
>10	≤5/50	88	48		
≤2	>5/50	100	50	–	46
2–5	>5/50	84	27	50	48
5–10	>5/50	45	15	14	29
10	>5/50	14	10		

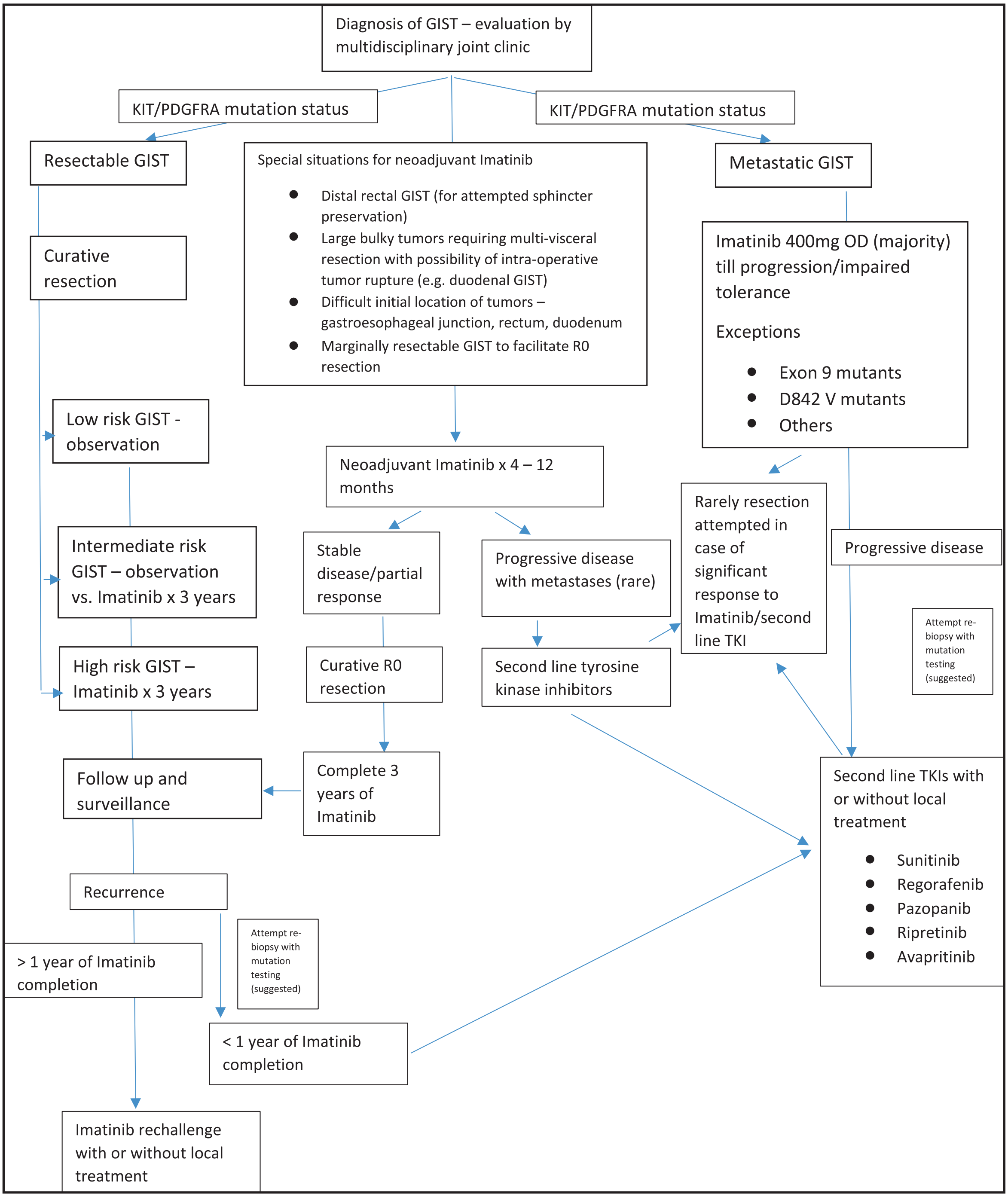
Diagnosis of GIST – evaluation by multidisciplinary joint clinic
KIT/PDGFRA mutation status
KIT/PDGFRA mutation status
Resectable GIST
Special situations for neoadjuvant Imatinib
Distal rectal GIST (for attempted sphincter preservation)
Large bulky tumors requiring multi-visceral resection with possibility of intra-operative tumor rupture (e.g. duodenal GIST)
Difficult initial location of tumors – gastroesophageal junction, rectum, duodenum
Marginally resectable GIST to facilitate R0 resection
Metastatic GIST
Curative resection
Imatinib 400mg OD (majority) till progression/impaired tolerance
Exceptions
Exon 9 mutants
D842 V mutants
Others
Low risk GIST - observation
Neoadjuvant Imatinib x 4 – 12 months
Rarely resection attempted in case of significant response to Imatinib/second line TKI
Intermediate risk GIST – observation vs. Imatinib x 3 years
Stable disease/partial response
Progressive disease with metastases (rare)
Progressive disease
Attempt re-biopsy with mutation testing (suggested)
High risk GIST – Imatinib x 3 years
Curative R0 resection
Second line tyrosine kinase inhibitors
Follow up and surveillance
Complete 3 years of Imatinib
Second line TKIs with or without local treatment
Sunitinib
Regorafenib
Pazopanib
Ripretinib
Avapritinib
Recurrence
> 1 year of Imatinib completion
Attempt re-biopsy with mutation testing (suggested)
< 1 year of Imatinib completion
Imatinib rechallenge with or without local treatment

Fig. 1 Management of GIST. Stage-wise management algorithm followed in TMH

6 Surgical Management

6.1 General Principles

Surgery is the primary treatment of choice for patients with localized or potentially resectable GIST lesions. Patients with resectable GIST may not require a preoperative biopsy, though every attempt should be made to obtain a biopsy in case of diagnostic dilemmas. A biopsy should be obtained in case neoadjuvant IM is being planned prior to attempted resection.

The surgical procedure aims at resecting the tumour with histologically negative margins (R0 resection), with segmental or wedge resections often being adequate. On laparotomy/laparoscopy, the abdomen should be thoroughly explored to evaluate peritoneal metastatic deposits. Primary GISTs may demonstrate inflammatory adhesions to surrounding organs, though true invasion is infrequent. GISTs are fragile tumours and should be carefully handled during resection to avoid tumour rupture. The goal is to achieve complete gross resection of the tumour with an intact pseudo capsule [36].

Lymphadenectomy is not indicated unless enlarged or pathologic nodes are seen on imaging or intraoperatively as GISTs rarely spread to regional nodes. Available evidence suggests that patients undergoing R0 or R1 resections have a similar prognosis, while patients with R2 resections have inferior outcomes [37]. The presence of microscopically positive margins (R1) after macroscopic total resection may not confer a worse prognosis. This is based on data from North America in more than 800 patients where there was no difference in recurrence-free survival in those who had R1 versus R0 resection [38].

6.2 Extent of Surgical Resection

Complete resection with at least a 1- to 2-cm gross margin should be the goal of surgical treatment.

Unlike other gastric tumours, gastric GISTs, usually require only a partial gastrectomy or even gastric wedge resection to achieve these margins. There is no oncological benefit in performing a total gastrectomy over a partial gastrectomy in gastric GISTs.

6.3 Minimally Invasive Approaches

Minimally invasive resection and open techniques are comparable in their outcomes in gastric GISTs. A meta-analysis of 19 studies ($n = 1060$ GIST cases) revealed no difference in long-term outcomes of GIST resections using laparotomy and laparoscopy. Laparoscopic resection in GISTs is also an acceptable standard of surgery [39–43]. Current guidelines prefer open surgeries for tumours greater than 5 cm in diameter. Unique to laparoscopic resections of GIST is the removal of the specimen within a closed system, such as a retrieval bag to avoid tumour spillage or seeding of port sites.

Three distinct minimally invasive approaches to resecting gastric GISTs based on tumour location in the stomach have been described and act as a basis for deciding the approach and extent of resection in these tumours [44].

6.4 Management of Small GISTs

GISTs ≥2 cm in size should be considered for resected, while there is equipoise on the management of tumours less than 2 cm in size. Endoscopic Mucosal Resection (EMR)And submucosal dissection (ESD) techniques can be occasionally employed in the management of few small GISTs. Gastric GISTs that are less than 2 cm in diameter and asymptomatic are currently referred to as very small, mini- (1–2 cm), or micro- (<1 cm) GISTs. Such tumours generally demonstrate benign clinical behaviour. However, lesions with high-risk features on EUS (irregular borders, cystic spaces, ulceration, echogenic foci, and internal heterogeneity) need adequate addressal due to their risks of progression. Current recommendations include initial evaluation with EUS for micro-GISTs, while EUS with or without CT is recommended for mini-GISTs. Subsequent follow-up is performed with serial EUS [45].

Surgery is required for lesions with high-risk features or those that increase in size on follow-up imaging.

6.5 Neoadjuvant Imatinib

Large abdominal tumours with a significant risk of tumour rupture during surgery are considered for treatment with preoperative IM. Tumours requiring complex surgical procedures or multivisceral resections are also considered for neoadjuvant IM after a multidisciplinary assessment [46–48].

The duration of preoperative medical therapy varies from 3 months to 1 year. Further detailing with regard to neoadjuvant imatinib therapy is mentioned in the medical management section of the chapter.

6.6 Unresectable, Recurrent, or Metastatic GIST

Surgery is rarely indicated in patients with metastatic GIST:

- Limited disease progression refractory to imatinib
- Initially unresectable tumours after a favourable response to imatinib.

- Management of symptomatic bleeding, obstruction, or similar local tumour-related complication.
- Liver limited metastatic disease where complete resection of disease can be achieved.

7 Medical Management

7.1 Brief History

The initial medical management of GIST is based on the role of imatinib mesylate (IM), a selective tyrosine kinase inhibitor of KIT, PDGFRA, and ABL. The significant response of a heavily pre-treated patient with GIST to IM followed by multiple trials highlighting responses and improved survivals with IM in GIST have ensured that IM is usually the first line of management in patients requiring systemic treatment [49].

7.2 Adjuvant Treatment Post Resection of GIST

The treatment of GIST post resection is assessed by the risk recurrence and prognostic scores previously discussed. Patients with very low-risk disease should be kept under surveillance/observation with no requirement of further treatment.

For patients with intermediate-risk GIST (recurrence risk 10–24%), adjuvant IM may or may not be considered [50–52]. However, there is a trend towards treating these patients with adjuvant IM for 3 years.

The evidence for the adjuvant treatment of resected GIST with IM was based on the ACOSOG Z9000 (Alliance) intergroup phase 2 trial. Patients labelled as ‘high risk’ tumours, (tumour diameter > 10 cm, intraperitoneal tumour rupture, or up to 4 peritoneal implants) received 1 year of adjuvant IM and showed improved 1-, 3-, and 5-year OS rate was 99, 97, and 83%, as compared to historical controls [53].The current standard of 3 years of adjuvant IM is based on the SSG XVIII Phase III trial, which showed that 3 years of adjuvant IM improved recurrence-free survival when compared to 1 year of adjuvant IM (65.6% vs. 47.9%; $p < 0.001$) [54]. A greater benefit with 3 years of IM was seen in patients with exon 11 mutations than other mutations, underscoring the importance of mutation testing in GIST [55]. Studies evaluating along duration of adjuvant IM are also being evaluated [51, 56].

The importance of mutation testing is also important in two specific scenarios. Firstly, GISTs harbouring the PDGFRA Exon 18/ D842V mutation (comprising 60–70% of PDGFRA mutants) are considered relatively resistant to IM and are considered for observation alone in these subgroup of patients [52, 57, 58]. Additionally, in KIT exon 9 mutants it may be worthwhile considering 800 mg/day as adjuvant therapy (based on the increased dose showing superior outcomes for this subset of tumours in the advanced setting) [52, 59].

7.3 Neoadjuvant Imatinib in GIST

Specific indications for the use of neoadjuvant IM are yet to standardized, but some scenarios where a neoadjuvant approach with IM is considered include:

- Anorectal GIST—for organ and/or sphincter preservation.
- Bulky GISTs in the duodenal-pancreatic region to reduce the extent of multivisceral resections and avoid intra-operative tumour rupture.
- Gastroesophageal junction, rectum, and duodenum GISTs where surgical access to tumours is difficult.
- Marginally resectable GIST to facilitate R0 resection.

Pooled data from the EORTC STBSG sarcoma group, in patients receiving neoadjuvant IM, showed that 83.2% of patients underwent R0 resection. Patients had received neoadjuvant IM for a period of 4–12 months [60]. The feasibility of neoadjuvant IM has also been shown with retrospective studies from Tata Memorial Hospital [48, 61].The Apollon phase II study prospectively evaluated the performance of neoadjuvant IM and showed high R0 resection rates and high PFS rates (3 year PFS—85.2%) [62]. Similar resection rates and survivals have been shown in other prospective studies as well [63].

The use of neoadjuvant IM has clinical implications in selective cases of GIST, though many questions in terms of duration of neoadjuvant IM, duration of adjuvant IM when neoadjuvant IM has been used and use of a higher dose in KIT exon 9 mutants remain to be answered [48].

7.4 Treatment of Advanced/Metastatic GIST

Patients with advanced/metastatic GIST have prolonged median survivals despite potentially advanced nature of disease. Patients with advanced GIST should have a KIT mutation testing and if required PDGFRA analysis while being planned for treatment.

The initial treatment for advanced/metastatic GIST is IM, with a dose of 400 mg/day recommended for KIT exon 11 mutants and 800 mg/day for KIT exon 9 mutants. This is based on patients with KIT exon 9 mutants deriving a PFS benefit when treated with 800 mg/day dosing [64]. Most patients respond to IM in a median of 3 months, though slower rate of responses is also known. The Choi criteria using PET scans can also be used for response assessment in GISTs [65].

Treatment with IM should be considered till progression, issues with tolerance, or patient choice [13]. The median progression-free survival with first-line IM in older series is approximately 18–24 months, though more recent series have shown an increased PFS of up to 3 years [10, 19, 60, 66, 67]. These differences can be explained by imatinib being used upfront current era and smaller tumours at diagnosis . There is also a select cohort of patients who will remain progression free for 6–10 years on IM alone [68].

Most patients with advanced GIST (approximately 80%) will progress after a median of 2–3 years, primarily due to the development of secondary KIT mutations [69]. Secondary mutations typically occur in the ATP binding pocket of KIT encoded by exons 13 and 14, and the activation loop (A-loop) encoded by exons 17 and 18 [70]. There is some evidence to suggest mutation status on progression may help guide second-line treatment options, i.e. sunitinib in KIT exon 13/14 mutant GISTs and regorafenib in secondary exon 17 mutants [71, 72].

Options post progression with IM include TKIs like sunitinib and regorafenib. Sunitinib (an oral multitargeted receptor tyrosine kinase inhibitor targeting KIT, PDGFRs, VEGFR-1, VEGFR-2, VEGFR-3, FLT3 and RET) has been shown to improve median time to progression as compared to placebo in the second line setting (27.3 weeks vs. 6.4 weeks; $p < 0.0001$) in a randomized setting and is currently recommended for the same [73]. Treatment with sunitinib requires monitoring, as there is an increased incidence of fatigue, diarrhoea, skin discolouration, and nausea seen with sunitinib. In patients who have progressed on both imatinib and sunitinib, the recommended option for further treatment is regorafenib (oral multikinase inhibitor inhibiting VEGFR1–3, TEK), KIT, RET, RAF1, BRAF, $\text{BRAF}^{\text{V600E}}$, PDGFR, and FGFR). The GRID study showed an improvement in PFS when regorafenib was compared to placebo (4.8 months vs. 0.9 months; $p < 0.0001$). The most common regorafenib-related adverse events of grade 3 or higher seen in the study were hypertension, hand-foot skin reaction, and diarrhoea, and these not to be kept a watch for.

While sequencing of treatment as mentioned above is preferable, options beyond this paradigm also need exploration. A commonly used treatment modality is increased dosing of IM from 400 mg to 800 mg per day [74]. Another strategy is evaluation of metastasectomy or resection in patients with limited progression [75, 76].

Sorafenib, dasatinib, and pazopanib have also shown limited activity in patients with advanced GIST [77–81].

7.5 Radiation Management

GIST is traditionally considered a radio resistant tumour [82]. Radiotherapy has shown to effect durable stabilization of the target lesions in some studies [83]. A few scenarios where radiotherapy may be attempted include [84]:

- Radiotherapy of metastases for palliation
- Radiotherapy of focally progressing lesions
- Definitive radiotherapy as an alternative to surgery in localized gist in elderly patients not feasible for surgery

8 Special Situations in GIST

8.1 Syndromes Associated with GIST

GIST is a predominantly sporadic disease, but germline mutations with familial predisposition to GIST have been identified [85, 86].

- Neurofibromatosis type 1; von Recklinghausen's disease (NF1): NF1 is an autosomal dominant hereditary disorder, with the mutated NF1 protein encoding the GTPase activating protein, neurofibromin. Approximately 34% of GI tract malignancies in patients with NF1 were GISTs. GISTs associated with NF1 have neither KIT nor PDGFRA mutations [87]. These tumours classically do not respond well to IM.
- Carney-Stratakis syndrome (CSS): CSS is an autosomal dominant syndrome with incomplete penetrance characterized by the development of paraganglioma, GIST, or both. Patients usually have mutations in succinic dehydrogenase (SDH)-B, C, and –D, with no mutations in KIT or PDGFRA.
- Carney's triad (CT): Carney's triad is a non-hereditary syndrome comprising paraganglioma, GIST, and pulmonary chordomas (atleast two of the three manifestations) [88]. These tumours do not have mutations in SDH, but have deletions of chromosome 1p and 1q12-q21, the site of the SDH-C gene. Mutations commonly associated with sporadic GIST are not found in these tumours. Tumours associated with CT are commonly seen in younger women, with frequent lymph node metastases, and multifocality.

Though the evidence is sparse, GISTs associated with the above-mentioned hereditary syndromes are generally less sensitive to treatment with IM [86].

8.2 Treatment of Advanced GIST with PDGFRA Mutations

Patients with PDGFRA mutations are seen in 5–15% localized GISTs, and 1–3% of advanced GISTs [89, 90]. Patients with resected disease and harbouring PDGFRA D842V mutations are considered for observation only. Evidence on these relative rare subsets comes from retrospective studies. The combined data from the European Organisation for Research and Treatment of Cancer (EORTC), Soft Tissue and Bone Sarcoma Group (STBSG), French Sarcoma Group (GSF-GETO), the Italian Sarcoma Group (ISG), and the Spanish Sarcoma Groups (GEIS) showed that patients harbouring the *PDGFRA-D842V* substitutions did not have responses to IM while those with other *PGFRA* mutations had responses to IM [91]. This also translated into markedly differing survivals between the two mutant cohorts. A second study from the Dutch group and North America, in contrast, suggested that a small cohort of patients with D842V mutants do respond to IM, though such patients would need frequent monitoring if started on IM [92]. A majority of patients with PDGFRA non-D842V respond to and should be treated with IM, while for patients with D842V mutations, the appropriate line of management at this juncture is still to be elucidated. Avapritinib is a relatively new drug that has shown encouraging results against all PDFGRA mutations and is to be considered in this setting.

9 Stage-Wise Prognosis with Current Management

The use of improved surgical techniques, early diagnosis of GIST, and systemic treatment with IM and other TKIs has improved survival across stages of GIST. The expected survival for patients receiving multimodality management in the current era is detailed in Table 2.

Table 2 Expected survival for patients receiving multimodality management

Stage	5-year overall survival (%) [90]
Low-risk and intermediate-risk resected GIST	91%
High-risk resected GIST	74%
Metastatic GIST	48%

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Renal Cancer

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Abbreviations

CNS	Central nervous system
CT	Computed tomography
HIFU	High-intensity focused ultrasonic ablation
LDH	Lactate dehydrogenase
MRI	Magnetic resonance imaging
nccRCC	Nonclear cell RCC
NSS	Nephron-sparing surgery
PFS	Progression-free survival
RCC	Renal cell carcinoma
RFA	Radiofrequency ablation
RN	Radical nephrectomy
TKI	Tyrosine kinase inhibitors
ULN	Upper limit of normal
USG	Ultrasonography
VEGF	Vascular endothelial growth factor

1 Introduction

Renal cell carcinoma (RCC) is an aggressive malignancy that comprises approximately 3% of all adult cancers, with a median age of 64 years at diagnosis. RCC accounts for 90% of renal tumors, with clear cell carcinoma being the most common histology [1, 2]. In contrast to developed countries where most of the patients present with small renal masses (<4 cm), in developing countries, large masses or metastatic disease is the more common form of presentation [3]. Surgery is the mainstay of treatment in localized and few locally advanced renal cancers, whereas systemic therapy has been shown to extend survival in advanced and metastatic cases. With newer targeted therapy and immunotherapy agents being approved at a rapid pace, the paradigm of management of RCC is ever-evolving.

2 Incidence and Epidemiology in India and Worldwide

According to the GLOBOCAN 2020 data, kidney cancer accounts for 2.2% of malignancies around the world with more than 400,000 new cases per year and more than 175,000 deaths [4]. RCC is more prevalent in developed countries as compared to developing countries with younger age at the time of diagnosis (median 56 years) in the latter [3]. As per the SEER database, the incidence of renal cell cancer is steadily increasing across all age and racial groups [5].

The data regarding RCC in India is scarce. Ray and colleagues in their retrospective review found that the mean age of presentation of RCC in India was 52.7 years, which is a decade earlier than that in western countries [6–9]. The male-to-female ratio ranges from 1.5:1 to 2.5:1 across various Indian studies. Common risk factors for RCC include smoking, obesity and hypertension, with the strongest evidence for smoking [2, 10]. Ray et al. [6] assessed five risk factors for RCC in Indian patients and found nearly 73.3% of patients had one or more risk factors including a history of occupational exposure in a few patients (printing, rubber, dye industry).

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3 Clinical Presentation

RCC may present in one of the following ways:

1. Asymptomatic—most of the small renal masses are detected incidentally on ultrasonography done for an unrelated abdominal complaint.
2. The traditionally described triad of symptoms (hematuria, flank mass and flank pain) is also called as the “too late triad” as it usually indicates advanced malignancy.
3. Symptoms suggestive of metastatic disease include bone pains, lymphadenopathy, dyspnea, cough, hemoptysis, jaundice, anorexia, weight-loss and fatigue.
4. Paraneoplastic syndromes are characteristically seen with RCCs in 20–30%. These include hypertension, erythrocytosis, hypercalcemia and jaundice.

In a large Indian series of RCC patients, most of the patients presented with symptomatic disease (80.7%) and incidental lesions were seen only in 9.3% [6].

4 Evaluation and Work-Up

4.1 Routine Laboratory Tests

These include complete blood count, renal and liver function tests, alkaline phosphatase and some other tests as needed, such as calcium, lactate dehydrogenase (LDH), electrolytes and urinalysis.

4.2 Radiology

1. *Abdominal USG*: This is usually the first investigation on which the mass has been detected. It is easily available and cheap [11]. The ultrasound can also distinguish between a solid and a cystic lesion. Further characterization of a cystic lesion would require axial imaging. A hyperechoic lesion, which suggests fat content, is almost diagnostic of an angiomyolipoma.
2. *Abdominal CT scan:* A contrast-enhanced CT scan of the abdomen and pelvis helps provide characterization of the renal mass and is the investigation of choice. A solid lesion that enhances more than 15 HU compared to the plain scan is almost diagnostic of an RCC. The Bosniak class of a cystic lesion can be determined which can help decide between observation vs. active intervention [12]. In a cystic lesion, thickened irregular walls or septa and solid enhancing areas are suggestive of malignancy. The CT scan will provide information to assign T, N and M staging to the renal mass. A note can be made of the anatomy of the renal vessels, presence of any tumor thrombus, loss of fat planes with any surrounding organs and presence of any hilar lymph nodes. All this information can aid in surgical planning. In a retrospective study of 100 RCCs patients by Johnson and colleagues, CT scan was found to have around 80–90% sensitivity and specificity for detection of renal vein invasion, metastatic lymphadenopathy and adjacent organ invasion except for detection of perinephric invasion where CT was found to have only 46% sensitivity [13].
3. *CT thorax:* This is performed to complete the metastatic evaluation and is superior to a chest x-ray [14]. Guidelines recommend performing a chest CT for all lesions which are larger than 4 cm in size.
4. *Magnetic resonance imaging (MRI):* A MRI scan may be performed if the patient has any contraindication to undergo a contrast-enhanced CT scan, like contrast allergy or reduced renal function. An MRI may also help in assessing for caval wall invasion in patients with IVC thrombus [15].
5. *Bone scan:* This is recommended only in patients who have bone pains or those with an elevated alkaline phosphatase level.
6. *Brain imaging:* An MRI brain should be performed in patients with neurological symptoms.
7. *Urine cytology:* This may be performed in patients with hematuria or those with a centrally located that is not intensely enhancing on the CT. Positive urine cytology will indicate a urothelial malignancy rather than an RCC. However, negative cytology does not rule it out.
8. *Renal biopsy:* Routine renal biopsy is not mandatory. The current role is in metastatic disease before initiation of systemic therapy or in the setting of a small renal mass, when active surveillance/ablative therapy is being contemplated instead of surgery. Other indications include a mass that is indeterminate for RCC on a CT scan, suspicion of lymphoma, metastasis from a different primary or an infective lesion [16].
9. *FDG PET scan:* Currently, PET alone has limited use for routine staging and follow-up for detecting relapse after nephrectomy in RCC [17].

4.3 Tumor Markers

The role of tumor markers in the diagnosis and management of RCC is currently very limited. In one particular study, high NSE (neuron-specific enolase) levels (examined by radioimmunoassay) were detected in 11 of 17 sera of patients with RCC. Positive rates for patients in stages II, III and IV were 100% (10/10) [18].

5 Pathology

RCCs were previously classified by cell type and growth pattern which has been changed to include morphology, growth pattern, cell of origin, histochemical and molecular findings to classify it into different subtypes. The current WHO classification system includes the following types of RCCs [19]:

1. Clear cell—70–80%.
2. Papillary—10–15%.
3. Chromophobe—3–15%.
4. Oncocytic—3–7%.
5. Renal medullary collecting duct.
6. Translocation associated [20].
7. Sarcomatoid variant; may be seen along with any of the above subtypes and carries a poor prognosis [21].

Classically, the Fuhrman grading system was for grading RCC. It is one of the most important histological prognostic factors but its prognostic value in nonclear cell RCC is unproven [22]. In a report by Tsui et al. the 5-year survival rates for tumors of histologic grade 1, 2 and 3 to 4 were 89%, 65% and 46%, respectively [23]. The widely used Fuhrman grading system has now been replaced by the International Society of Urological Pathology (ISUP) classification which relies solely on nucleolar prominence for grades 1–3, leading to less interobserver variation. Any presence of rhabdoid or sarcomatoid elements classifies a tumor as grade 4 in the ISUP system and is an indicator of poor prognosis.

6 Genetic Evaluation

Five to 8% of RCCs are hereditary. Hereditary RCC syndromes have distinct clinical and molecular phenotypes. Guideline recommendations for genetic counseling in RCC patients are as follows [24]:

1. Patients with any renal tumor (benign or malignant) and any one of the following:
    (a) Bilaterality or multifocality
    (b) Early age of onset (</= 45 years of age)
    (c) First- or second-degree relative with any renal tumor
    (d) One of the following associated tumors:
        - Pheochromocytoma/paraganglioma
        - Hemangioblastoma of retina, brain stem, cerebellum, spinal cord
        - Early-onset multiple uterine fibroids (<30 years of age)
2. Patient with nonclear renal cell carcinoma with unusual associated features (chromophobe, oncocytic or hybrid tumor)
3. Patients with or without RCC who report a family member (any) with known clinical or genetic diagnosis of any one of the following
    (a) Von Hippel–Lindau (VHL) syndrome
    (b) Birt–Hogg–Dube syndrome
    (c) Hereditary leiomyomatosis and renal cell cancer
    (d) Hereditary papillary renal cell cancer
        - *Staging* of renal cancer [25] can be found in the AJCC Cancer Staging Manual, Eighth Edition, Chapter 60, page no. 743–44, which can be accessed at https://emedicine.medscape.com/article/2006851-overview.

7 Anatomical Classification Systems

Various scoring systems, such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) score, the R.E.N.A.L. nephrometry score, the C-index, an Arterial-Based Complexity (ABC) Scoring System and Zonal NePhRO scoring system, have been described. THE RENAL nephrometry score is most commonly used and includes the following components:

- R: Radius. This scores the tumor size as its maximal diameter in mm
- E: Exophytic/endophytic component of the tumor
- N: Nearness of the tumor to the collecting system or renal sinus
- A: Anterior (a)/posterior (p) location of the tumor
- L: Location relative to the polar lines

Each individual component is assigned a score ranging from 1 to 3, for a total score ranging from 4 to 12. The suffix “x” is used when it is not possible to assign “a” or “p” to the tumor. An additional suffix “h” is used to indicate that the tumor abuts hilar structures.

Such scoring of renal masses allows the comparison of data across various reports and objective prediction of potential complications with nephron-sparing surgery and ablative techniques. It helps in choosing between partial vs. radical nephrectomy, choosing the approach to surgery and in patient counseling.

8 Principles of Management

The most important step in planning management is to accurately stage of the disease. In localized and certain locally advanced cases, surgical resection with curative intent is the mainstay of treatment—either in the form of a radical nephrectomy or NSS. The choice between the two is governed primarily by tumor factors (size and location) and patient factors (age, comorbid status, bilateral tumors) and partly by surgeon experience and skill. Following surgery, patients are kept on a strict follow-up schedule, the intensity of which depends on the pathological stage of the tumor. There is limited promising data available on the survival ben-

Table 1 Guidelines for management of localized or locally advanced RCC [26]

All clinically T1 tumors should undergo partial nephrectomy unless risk of margin positivity or any comorbidities precludes partial nephrectomy.
When partial nephrectomy not feasible, radical nephrectomy with preferred minimal invasive technique is treatment for organ confined RCC (stages T1T2N0NxM0).
For all radical nephrectomies, adrenalectomy and lymph node dissection are not recommended routinely.
In locally advanced RCC, open radical nephrectomy with goal of obtaining negative margins is still the standard of care.
Patients with small cortical tumors (≤ 3 cm) and age > 70 years, high surgical risk, solitary kidney, compromised renal function, hereditary RCC or multiple bilateral tumors ablative treatment can be considered.

efit of adjuvant therapy for high-risk tumors. The role of cytoreductive nephrectomy has declined following the publication of two major randomized controlled trials. However, it is still considered in the setting of a good-risk metastatic patient who can be offered metastasectomy at the same time. In unresectable locally advanced and intermediate/poor-risk metastatic disease, targeted or immunotherapy following a renal mass biopsy is the norm. (Table 1).

9 Surgical Management

9.1 Stage 1, 2 Disease (Tumor Limited to the Kidney)

9.1.1 Principles of Radical Nephrectomy (RN)

1. Early ligation of renal artery followed by the vein.
2. Removal of kidney along with the perinephric fat enclosed by the Gerota's fascia.
3. Ipsilateral adrenalectomy: Although this was classically described, the current practice is that the ipsilateral adrenal gland is removed only if there are any features of invasion on imaging or during intraop palpation of the gland.
4. Regional lymphadenectomy—Current evidence states that regional lymphadenectomy has only staging benefit and no therapeutic benefit. The only randomized controlled trial which evaluated the role of lymph node dissection in RCC did not find any survival benefit. However, the trial had some limitations one of which was that it included a substantial proportion of patients with <T3 disease and the incidence of lymph node metastasis in these patients is anyways very low [27]. The traditionally recognized features which should prompt one to perform a regional lymph nodal clearance in RCCs include tumor size >10 cm, T3–T4 tumors, grade 3–4 and evidence of tumor necrosis on imaging or on biopsy [28, 29].

Radical nephrectomy may be performed by one of the following approaches. None of them have any oncological benefit over the other. Choice of approach is again dictated by tumor factors, patient factors (age, comorbid status, BMI, affordability) and the surgeon's own experience and comfort with a particular approach:

1. Open: May be transperitoneal or retroperitoneal. The choice of incision depends on the size and location of the tumor and the comfort of the surgeon.
2. Laparoscopic: Transperitoneal, retro-peritoneal or hand assisted.
3. Robotic: Transperitoneal and extraperitoneal.

9.1.2 Nephron-Sparing Surgery

The indications for NSS are as follows:

Absolute: An anatomically or functionally solitary kidney where radical nephrectomy would render the patient anephric.

Relative:

1. If the contralateral kidney is affected by a condition which may compromise its function in the future such as diabetic nephropathy, calculus disease, hypertension.
2. Hereditary RCC—Increased risk of developing a contralateral renal tumor.
3. Elective—It is the treatment of choice in cT1a lesions and may also be offered in select cT1b and T2a tumors, depending on the surgeon's experience.

Various centers have reported excellent cancer-specific survival following NSS and as such, NSS is oncologically noninferior to radical nephrectomy [30–32]. A single-cell-negative margin has been shown to be sufficient, and this allows for enucleation of tumors in addition to other techniques like resection and enucleoresection [33]. Minimally invasive partial nephrectomy, either laparoscopic or robot-assisted, has also been described with comparable results and much faster patient recovery.

9.1.3 Ablative Techniques

Ablative procedures may be considered in the following settings:

- Elderly patients with significant comorbidities who have been deemed as having a high risk for a surgical procedure.
- Small incidentally detected tumors (only cT1a).
- Patients with bilateral tumors or tumor in a solitary kidney.

Ablative techniques include radiofrequency ablation (RFA), cryotherapy, microwave and high-intensity focused ultrasonic ablation (HIFU). A recent population-based study compared survival after surgery vs. nonsurgical management for small renal masses and noted that the recurrence-free survival was lower with these ablative techniques [34].

9.2 RCC with Tumor Thrombus (Extending to Renal Vein or Inferior Vena Cava [4–10%])

Tumor thrombi are classified as follows based on the cranial limit of the thrombus:

0: Thrombus within the renal vein only.

I: Thrombus extends into the IVC but for <2 cm from the renal vein ostium.

II: Thrombus extends up to lower border of liver (infrahepatic).

III: Thrombus extends into the intrahepatic portion of the IVC but below the diaphragm.

IV: Thrombus extends above the diaphragm.

Level III/IV thrombi may be associated with advanced locoregional disease and have poorer prognosis. Surgery remains the mainstay of treatment for RCCs with tumor thrombus and excellent 5-year survival of 40–70% has been reported with complete excision [35]. There have been reported attempts at shrinking the tumor thrombus with the use of neoadjuvant targeted therapy/immunotherapy. However, these are small reports and have shown a very modest response rate. Neoadjuvant therapy may be tried in case the tumor along with the thrombus is deemed unresectable on imaging.

9.3 Surveillance Following Surgery for RCC

There are no evidence-based surveillance guidelines. Various scoring systems are available which help to estimate the risk of recurrence in patients who have treated with a curative intent and this helps decide the intensity of surveillance. One of the commonly employed follow-up surveillance schemes is presented in Table 2 [36].

10 Medical Management

10.1 Adjuvant Treatment for Localized RCC

Various trials have evaluated the role of targeted therapy agents in the adjuvant setting. One of these studies (the S-TRAC trial) showed a disease-free survival benefit (median 6.8 years with sunitinib vs. 5.8 years in the observation arm) and on the basis of this result, sunitinib may be offered to patients who are at a high risk of relapse (pT3/4 or pN+ or those with grade 3/4) [37]. However, sunitinib is associated with significant toxicity and thus is not routinely used in the adjuvant setting. Moreover, the trial did not show any overall survival benefit. Various other trials evaluated other agents in the adjuvant setting like pazopanib, sorafenib and axitinib but none of them were able to demonstrate any survival benefit [38]. Recently, the KEYNOTE-564 trial published its results where 1 year of adjuvant pembrolizumab (17 three-weekly doses of 200 mg iv pembrolizumab) showed a disease-free survival benefit of 9% at 2 years (77% vs. 68%) and is now FDA approved for this indication. The high cost of this therapy is a major deterrent for its use.

11 Radiation Therapy

RCC has traditionally been considered to be an inherently radio-resistant tumor. However, there are recent reports of using Stereotactic Body Ablative Radiotherapy (SBRT) for small renal masses, with encouraging results. However, the use of radiation therapy for renal masses remains investigational at present and is not recommended for routine clinical practice. Another application of radiation therapy in RCC is in the setting of metastatic disease where it may be used in the ablation of small/few lung or bone metastasis in an attempt to achieve metastasectomy good-risk patients and also for palliation of painful bone metastasis and brain lesions.

Table 2 Recommendation of surveillance based on current guidelines

	Postoperative months								
	3	6	12	18	24	30	36	48	60
Low risk/T1									
Hx, PE and blood test	X		X		X		X	X	X
CHEST			CT		CXR		CT	CXR	CT
ABDOMEN	CT		CT/US		CT/US		CT/US		CT/US
Intermediate risk/T2									
Hx, PE and blood test	X	X	X	X	X	X	X	X	X
CHEST		CXR	CT	CXR	CT	CXR	CT	CXR	CT
ABDOMEN	CT	US	CT	US	CT	US	CT	US	CT
High risk/T3									
Hx, PE and blood test	X	X	X	X	X	X	X	X	X
CHEST		CXR	CT	CXR	CT	CXR	CT	CXR	CT
ABDOMEN	CT	CT	CT	CT	CT	CT	CT	CT	CT

Hx history, *PE* physical examination, *CXR* chest X-ray, *US* ultrasound

12 Stage-Wise Management Algorithms (Figs. 1 and 2)

13 Stage-Wise Prognosis (Table 3) [39]

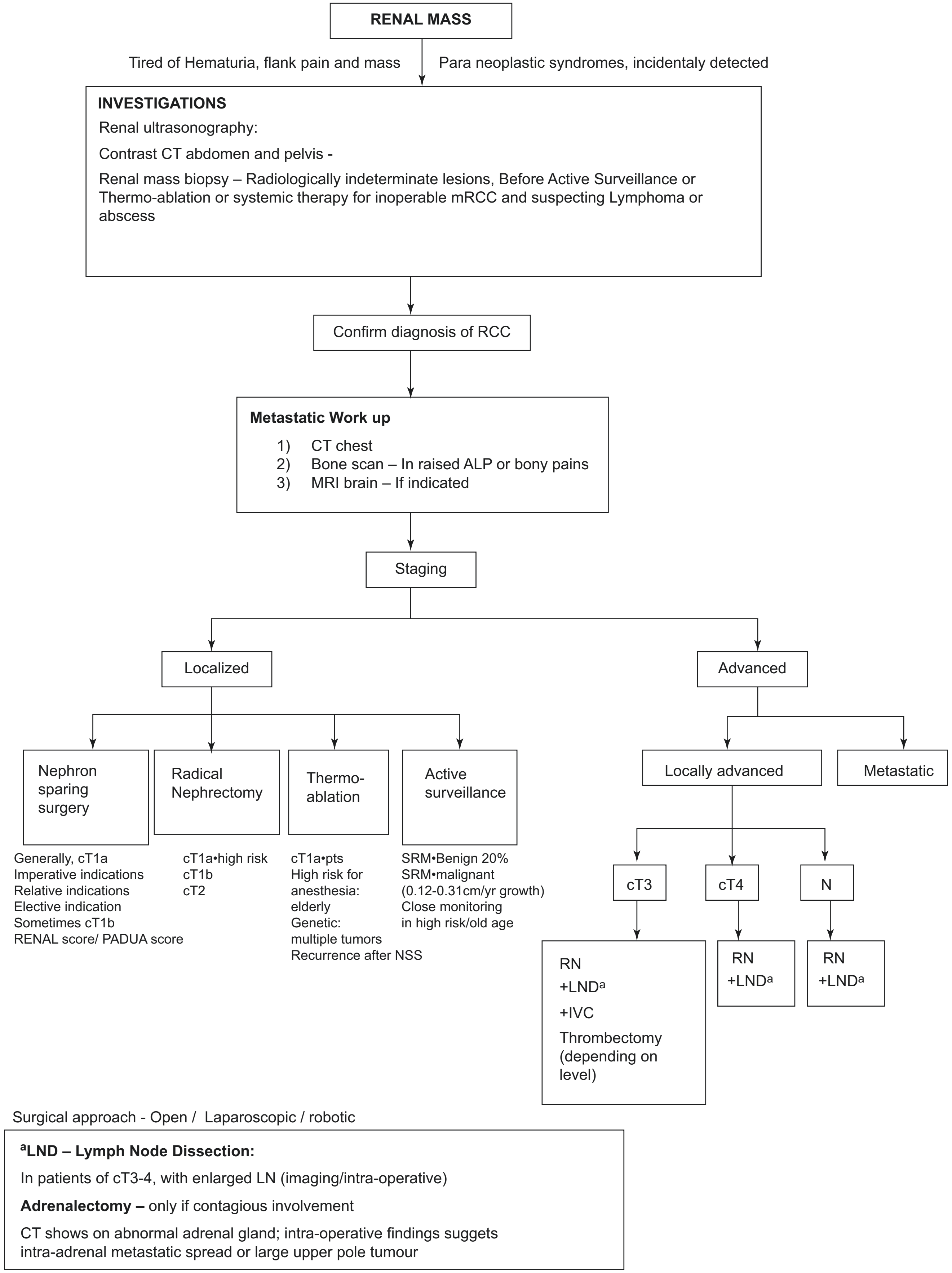
RENAL MASS
Tired of Hematuria, flank pain and mass
Para neoplastic syndromes, incidentaly detected
INVESTIGATIONS
Renal ultrasonography:
Contrast CT abdomen and pelvis -
Renal mass biopsy – Radiologically indeterminate lesions, Before Active Surveillance or Thermo-ablation or systemic therapy for inoperable mRCC and suspecting Lymphoma or abscess
Confirm diagnosis of RCC
Metastatic Work up
1) CT chest
2) Bone scan – In raised ALP or bony pains
3) MRI brain – If indicated
Staging
Localized
Advanced
Nephron sparing surgery
Radical Nephrectomy
Thermo-ablation
Active surveillance
Generally, cT1a
Imperative indications
Relative indications
Elective indication
Sometimes cT1b
RENAL score/ PADUA score
cT1a•high risk
cT1b
cT2
cT1a•pts
High risk for anesthesia:
elderly
Genetic:
multiple tumors
Recurrence after NSS
SRM•Benign 20%
SRM•malignant
(0.12-0.31cm/yr growth)
Close monitoring
in high risk/old age
Locally advanced
Metastatic
cT3
cT4
N
RN +LNDa +IVC Thrombectomy (depending on level)
RN +LNDa
RN +LNDa
Surgical approach - Open / Laparoscopic / robotic
aLND – Lymph Node Dissection:
In patients of cT3-4, with enlarged LN (imaging/intra-operative)
Adrenalectomy – only if contagious involvement
CT shows on abnormal adrenal gland; intra-operative findings suggets intra-adrenal metastatic spread or large upper pole tumour

Fig. 1 Flow chart for localized and locally advanced RCC

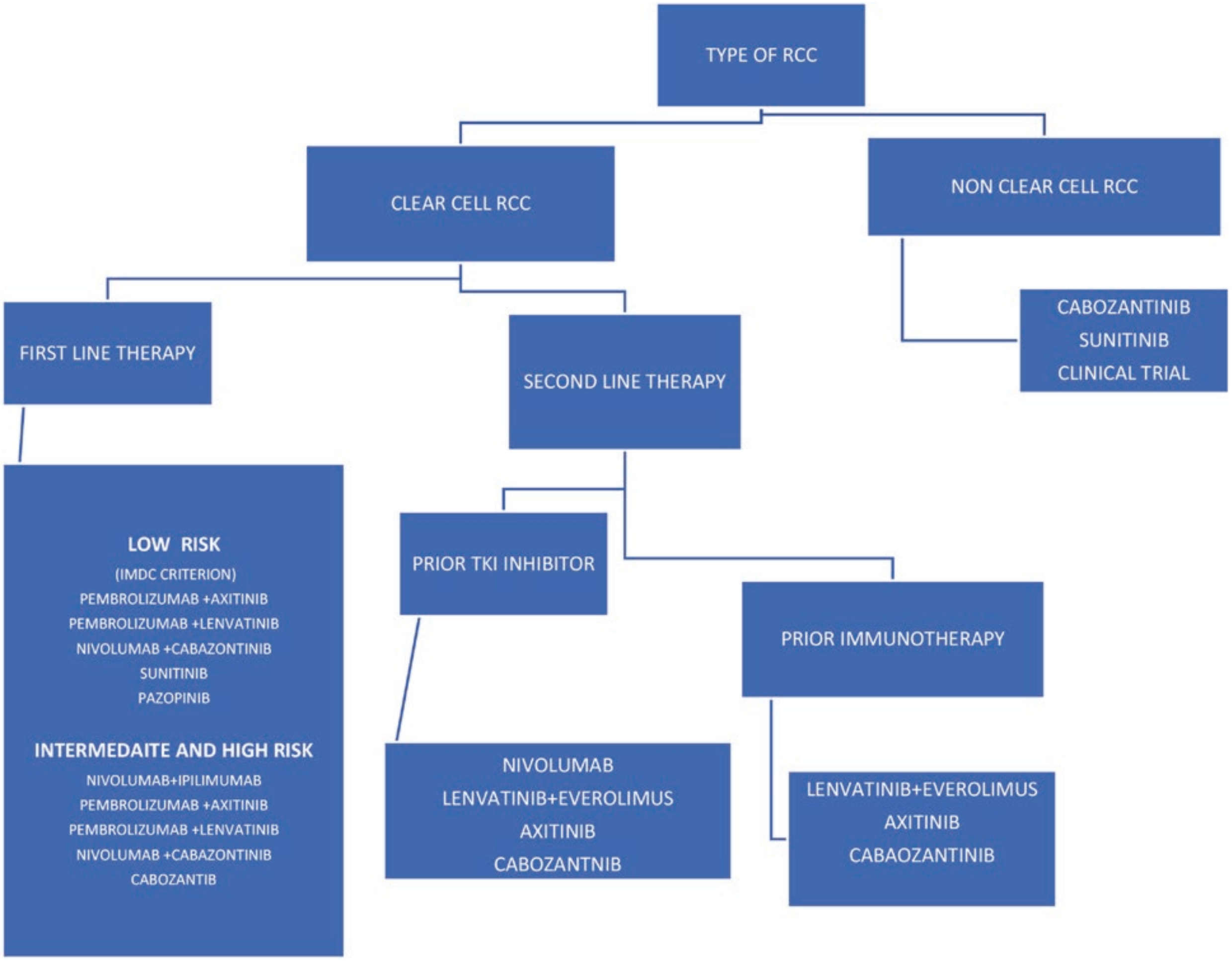
TYPE OF RCC
CLEAR CELL RCC
NON CLEAR CELL RCC
CABOZANTINIB
SUNITINIB
CLINICAL TRIAL
FIRST LINE THERAPY
SECOND LINE THERAPY
LOW RISK
(IMDC CRITERION)
PEMBROLIZUMAB +AXITINIB
PEMBROLIZUMAB +LENVATINIB
NIVOLUMAB +CABAZONTINIB
SUNITINIB
PAZOPINIB
INTERMEDAITE AND HIGH RISK
NIVOLUMAB+IPILIMUMAB
PEMBROLIZUMAB +AXITINIB
PEMBROLIZUMAB +LENVATINIB
NIVOLUMAB +CABAZONTINIB
CABOZANTIB
PRIOR TKI INHIBITOR
PRIOR IMMUNOTHERAPY
NIVOLUMAB
LENVATINIB+EVEROLIMUS
AXITINIB
CABOZANTNIB
LENVATINIB+EVEROLIMUS
AXITINIB
CABAOZANTINIB

Fig. 2 Flow chart for management for metastatic RCC

Table 3 Stage-wise prognosis

Stage	5-year survival (%)
I	96
II	82
III	64
IV	23

14 Management of Metastatic Disease

The first step in the management of metastatic RCC is to risk stratify patients as the entire spectrum of metastatic RCC is very heterogeneous. Various risk stratification models have been developed by combining independent prognostic factors. The first such prognostic model was developed by the Memorial Sloan Kettering Cancer Center (MSKCC). It was based on a cohort of patients who were treated with interferons [40]. Eventually, interferons were replaced by tyrosine kinase inhibitors. Hence, in the new era of VEGF-targeted therapies, a new risk stratification model was developed and is known as the International Metastatic RCC Database Consortium (IMDC) model [41]. This model retained four of the five prognostic factors previously identified by MSKCC. It excluded LDH and added two more adverse prognostic factors, namely, absolute neutrophil count greater than the upper limit of normal (ULN) and platelets greater than the ULN. In the IMDC model, patients with none, 1–2 and 3 or more risk factors were classified as favorable, intermediate- and poor-risk patients respectively, and their median survival ranged from 43 months, for favorable risk to 22 months for intermediate-risk and a dismal 8 months for poor risk.

Cytoreductive nephrectomy (CN) before systemic therapy had been the traditional standard of care in patients with a resectable primary tumor and this practice was supported by large studies. A combined analysis of the SWOG and EORTC randomized trials showed that patients who underwent CN also received IFN-α had a median survival of 13.6 months compared to 7.8 months in patients who received IFN-α alone [42]. However, all these prior studies were performed in patients who had been treated with IFN-α; and the role of CN in the era of targeted therapy, which is more efficient than IFNs, was unclear [43]. The recently published CARMENA trial randomly assigned 450 patients in a 1:1 ratio to either receive sunitinib alone (intervention arm) or undergo a CN followed by sunitinib (standard arm). It was found that sunitinib alone was noninferior to CN followed by sunitinib. Not all patients who underwent CN were able to receive sunitinib due to postoperative morbidity. Thus, the trial concluded that metastatic RCC patients should be started on targeted therapy and a CN may be considered later in responders. This strategy would ensure that all patients receive systemic therapy which is pivotal in the management of metastatic cancer. However, a major limitation of this trial was that it included only intermediate- and poor-risk patients. Thus, the ideal treatment strategy for good-risk patients remains to be defined. Guidelines recommend CN for good-risk patients especially if the metastatic sites can also be treated either by resection or SBRT, which can render the patient as "no evidence of disease (NED)." Further evidence suggests that even intermediate-risk patients with only one adverse risk factor may benefit from CN [44].

15 Systemic Therapy for Metastatic RCC

15.1 Targeted Therapy

The discovery of VHL mutations and the activation of VEGF, PDGF and other genes involved in angiogenesis, cell growth and survival led to the development of several targeted therapies that have improved the clinical outcomes of patients with metastatic RCC.

For a long time, *sunitinib* (against the VEGF receptors, PDGF receptors and other kinases) had been the first-line therapy for the treatment of patients with upfront metastatic RCC based on the results of a phase III trial by Motzer et al. [45]. Sunitinib 50 mg/day (4 weeks on and 2 weeks off) produced a significantly higher objective response rate than IFN-α (31% vs. 6%). Later, updated results of this trial showed a trend toward better OS with sunitinib over IFN-α (26.4 months vs. 21.81 months, $p = 0.051$). To manage the toxicity associated with sunitinib, alternate regimens have also been tried which have used 2 weeks on and 1 week off.

Pazopanib (multitargeted, small-molecule TKI) was evaluated in a randomized phase III trial (2:1 for pazopanib or placebo) and it was shown to significantly prolong the progression-free survival (9.2 months vs. 4.2 months) [46]. A large noninferiority trial compared sunitinib and pazopanib (COMPARZ) showed that although the two drugs have comparable efficacy (median PFS was 9.5 months for sunitinib vs. 8.4 months for pazopanib), pazopanib had a better side-effect profile and was associated with lesser incidence of fatigue, hand-foot syndrome and thrombocytopenia [47]. In an another patient-preference study, pazopanib was preferred by patients in view of better tolerability.

Bevacizumab, an angiogenesis inhibitor and monoclonal antibody against VEGF, in addition to IFN-α was compared with placebo plus IFN-α. A significantly longer PFS (10.2 vs. 5.4 months) was seen with the combination with no significant increase in side-effects [48]. Bevacizumab is rarely used in today's practice due to the availability of much more efficacious agents.

Almost all trials evaluating sunitinib and pazopanib included only MSKCC good and intermediate-risk patients, and thus, the results of those trials could not be extrapolated to patients belonging to the poor-risk category. In a retrospective study, sunitinib resulted in median OS of 8.16 months in poor-risk patients [49].

Another TKI, *cabozantinib* was compared with Sunitinib in a phase 2 randomized trial (CABOSUN) which included 157 first-line intermediate- and poor-risk metastatic RCC patients. Cabozantinib showed a significantly improved PFS (median 8.2 vs. 5.6 months) and was associated with a higher objective response rate of 46% vs. 18% for sunitinib. However, this did not translate to any OS benefit [50].

Axitinib, an oral selective inhibitor of VEGF was compared in the AXIS trial to sorafenib in patients who had failed on sunitinib. Axitinib therapy resulted in a longer PFS (median 4.8 vs. 3.4 months); however, this did not translate into OS benefit [51]. Axitinib was also compared to sorafenib in a phase 3 RCT as first-line therapy for metastatic RCC; however, no significant difference in the PFS was seen [52].

Lenvatinib is an oral inhibitor of VEGF and PDGF and also has inhibitory activity against fibroblast growth factor receptors (FGFRs). It has been evaluated in combination with everolimus and is discussed below under the section of combination therapies [53].

15.2 Immune Checkpoint Inhibitors-Based Combination Therapies

Immune checkpoint inhibitors-based combination therapy has superseded single agent targeted therapy as the first-line therapy for metastatic RCC. Various combinations have been evaluated in large phase 3 RCTs and are summarized below.

1. CheckMate 214 trial (NCT 02231749) *Nivolumab (programmed death 1 (PD-1) inhibitor antibody) plus Ipilimumab (anti-cytotoxic T-lymphocyte associated antigen 4 antibody)* vs. *sunitinib* [54].

   This trial included only IMDC intermediate- and poor-risk patients and the combination therapy showed an OS benefit with an HR of 0.63. These results led to a paradigm shift in the management of metastatic RCC. A recent with 60-month follow-up showed a 5-year OS probability of 43% for the combination vs. 31% for sunitinib [55].

2. KEYNOTE-426 trial (NCT02853331) *Combination of axitinib plus pembrolizumab (PD-1 inhibitor)* vs. *sunitinib* [56].

   Median OS for the combination was significantly longer at 45.7 months compared to 40.1 months for sunitinib. Subgroup analysis revealed that the OS was similar in the favorable subgroup while an OS benefit was seen with the intermediate- and poor-risk patients. The PFS benefit (HR 0.68; 95% CI: 0.58–0.80) was seen across all risk groups. Treatment efficacy was seen regardless of PD-L1 status.
3. CheckMate 9ER trial (NCT03141177) *Combination of nivolumab plus cabozantinib* vs. *sunitinib* [57].

   The combination significantly prolonged the PFS compared to sunitinib (16.6 months vs. 8.3 months). A significant benefit was also seen with OS (HR 0.60; 95% CI: 0.40–0.89) at a median follow-up of 18 months. Efficacy of this combination was seen across all risk groups and irrespective of PD-L1 status. Severe side-effects (grade 3 and more) were seen in 61% receiving the combination vs. 51% receiving sunitinib alone.
4. CLEAR trial (NCT02811861) *Lenvatinib + Everolimus or Lenvatinib + Pembrolizumab* vs. *Sunitinib Alone* [58].

   The Lenvatinib plus pembrolizumab combinations showed a significantly longer PFS compared to sunitinib alone (median 23.9 months vs. 9.2 months). An OS benefit was also seen with this combination (HR 0.66; 95% CI: 0.49–0.88). The lenvatinib plus everolimus combination did demonstrate a longer PFS (median 14 months) compared to sunitinib alone; however, no OS benefit was seen with this combination.
5. JAVELIN trial (NCT02684006) *Avelumab plus axitinib* vs. *sunitinib* [59]

   This combination did show PFS benefit compared to sunitinib in patients who were PD-L1 positive. However, the OS data is yet to mature and this combination is not recommended by guidelines yet.

It is important to note that all the above combination therapies have been evaluated against single-agent sunitinib. There is no prospective data comparing any of the combinations and as such, no recommendation can be made for one particular combination over the others. The decision of choosing a particular combination for a particular patient depends on the patient's tolerability with regards to any specific side-effects of any agent, affordability and availability issues and finally, on the clinician's acumen. This particular field in the management of metastatic RCC is ever evolving and newer agents and their combinations are getting approval based on robust phase 3 RCT data. As of May 2022, the agents recommended by guidelines for first-line management of metastatic clear cell RCC are summarized in Table 4. For subsequent therapy following progression, out of TKI and immunotherapy, whichever agent was not used in first-line therapy, may be tried. For third-line therapy, only cabozantinib has data from a phase 3 RCT and may be used preferentially if not used earlier.

Table 4 Guideline recommendations for first-line therapy in metastatic clear cell RCC

Risk category	Preferred regimens	Other regimens
Favorable	Pembrolizumab + Axitinib Cabozantinib + Nivolumab Pembrolizumab + Lenvatinib	Cabozantinib Pazopanib Sunitinib
Intermediate/poor	Pembrolizumab + Axitinib Cabozantinib + Nivolumab Pembrolizumab + Lenvatinib Nivolumab + Ipilimumab	Cabozantinib Pazopanib Sunitinib

15.3 Nonclear Cell metastatic RCCs

There is no phase 3 RCT data available to provide any recommendations for nonclear cell metastatic RCCs. The ASPEN study was a phase 2 trial that evaluated everolimus vs. sunitinib in 108 such patients. Those treated with sunitinib had a significantly better PFS compared to everolimus (8.3 months vs. 5.6 months), and thus, sunitinib may be used as the preferred agent in these patients [60].

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Adrenocortical Carcinoma

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Abbreviations

ACC	Adrenal cortical carcinoma
CT	Computed tomography
ENSAT	European Network for the Study of Adrenal Tumors
HGF	Hepatocyte growth factor
IGF-2	Insulin-like growth factor 2
LFS	Li–Fraumeni syndrome
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
OA	Open adrenalectomy
PET	Positron emission tomography
TNM	Tumor-node-metastasis

1 Introduction

Adrenal cancer, also known as carcinoma, is a rare but aggressive malignancy that affects people of all ages. In many cases, the diagnosis occurs in the metastatic stage. The investigations are primarily used to stage the disease and determine whether the adrenal cancer is secreting hormones or this is a non-secretary tumor. Treatment options can be complex, and multimodality treatment is beneficial. Optimal care is offered with the involvement of surgical oncologists, medical oncologists, endocrinologists, and radiation oncologists.

2 Incidence and Epidemiology: Global and India

Adrenal cortical carcinoma (ACC) is uncommon cancer with an aggressive course with poor outcomes. The reported annual incidence is about 1–2 cases per million [1]. In the United States, as per the Surveillance, Epidemiology, and End Results (SEER) database, the incidence is 0.7 cases per million per year and 0.2% of all cancer deaths [2, 3]. ACC has two peaks in early childhood and second in the fourth and fifth decades of life, although this can affect any age with a slightly increased female preponderance [3].

3 Genetic Predispostion

3.1 Inherited/Germline

ACC in childhood is usually associated with various genetic disorders affecting TP 53 mutation and alternation in the insulin-like growth factor 2 (IGF-2). This is commonly seen in patients having Li–Fraumeni syndrome (50–80% of pediatric ACC), Beckwith–Wiedemann syndrome, multiple endocrine neoplasia Type 1, Carney complex, and congenital adrenal hyperplasia. Lynch syndrome also has an association with ACC as reported in a series of 114 patients diagnosed with ACC, 3.2% have underlying Lynch syndrome. Patients of ACC with Lynch syndrome may have MSH2, MLH1, and MSH6 germline mutations [4].

3.2 Acquired

In most adult-onset ACC, either there is TP53 inactivating mutation or activating mutations of the proto-oncogene b-catenin (CTNNB1) or [5, 6] ZNRF3 (zinc and ring finger protein 3) gene mutation, which is involved in the Wnt signaling pathway [6]. Chromosomal gains, detected by comparative genetic hybridization at 5, 7, 12, 16, 19, and defeats

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at 13 and 22, have also been seen along with the hypermethylation of specific gene promoters in H19, PLAGL1, G0S2, and NDRG2. Recently, micro RNA specifically, upregulation of miR-483 and an ACC miR-195 and miR-335 downregulation has also been seen in a few cases of ACC [7].

With the evolving data of TCGA (The Cancer Genome Atlas), a few new genes such as PRKAR1A, RPL22, and TERF2 were also associated with ACC. Telomere maintenance, specially TERF2, plays a vital role in developing ACC [8]. Although IGF-2 is overexpressed in the majority of the ACC; still, the IGF-1 receptor-mediated downstream pathway which activates the protein kinase B Akt/mechanistic target of the rapamycin (mTOR) does not have a role in the pathogenesis of ACC. This hypothesis has also been further proved as IGF-1R/mTOR signaling pathway inhibitors have not shown any benefit in ACC patients. Other pathways, such as hepatocyte growth factor (HGF) and cMET, have been activated in ACC. The different path that has been activated is HGF/cMET, which is associated with its downstream way, leading to increased cell proliferation, apoptosis inhibition, angiogenesis, resistance to chemotherapy, and finally, cell survival [9].

4 Clinical Presentation: Global and India

Approximately half of ACC patients present with signs and symptoms of increased hormone production by the tumor, including clinical Cushing's syndrome and female virilization [10]. Rest one-third present with local symptoms due to tumor growth and involvement of adjacent organs; this can include abdominal fullness, early satiety, and dull aching pain radiating to the back (9, 10). Rest 30% of ACCs are diagnosed when imaging is done for unrelated issues; these are the incidentally detected ACC and mostly non-secretary types. Although estrogen hypersecretion is rare (1–3%), this can lead to gynecomastia and testicular atrophy. This is pathognomonic for ACC [11]. Childhood ACCs are more hormone secreting as compared to adult patients. In children, the adrenal cortex's persistent fetal zone produces dehydroepiandrosterone sulfate (DHEA-S), leading to virilization [12].

5 Evaluation and Work-Up

5.1 Biochemical

Most ACC secrete hormones; hence, comprehensive endocrine assessment is an integral component of any suspected adrenal mass lesion in the preoperative workup. Biochemical workup helps establish or exclude the diagnosis of excess hormone production, the adrenocortical origin of a tumor, future follow-up, and surveillance, and assessing the requirement of postsurgical hydrocortisone therapy. European Network for the Study of Adrenal Tumors (ENSAT) has proposed the panel of hormones in a suspected case of ACC of excess glucocorticoids (basal cortisol and 1 mg dexamethasone suppression test), sex steroids and their precursor (DHEA, 17- hydroxyprogesterone, androstenedione, testosterone in women, 17-beta-estradiol in men, 11-deoxycortisol minerlocorticoids excess (aldosterone/renin ratio, serum potassium), and also plasma-free metanephrines or urinary fractionated metanephrines to rule out pheochromocytoma [13].

5.2 Radiology

CT scan, USG abdomen, MRI scan, and PET CT are used to evaluate adrenal lesions with the pros and cons of each modality.

Imaging is done for staging and tumor relationship with the surrounding organs and vessels to assess the possibility of surgery and determine the therapy response in case of metastatic disease during follow-up. Three-dimensional reconstruction of CT or MRI images helps to understand better the morphology and relationship of ACCs with the surrounding structure and subsequent decision for open versus laparoscopic removal of the tumor [14].

Computed tomography: CT scan of the abdomen and pelvis is the most commonly used first choice. Typical features of ACC which differentiate ACC from adrenal adenoma include the large size of the tumor, irregular borders, areas of necrosis, hemorrhage, and calcification leading to heterogeneous appearance and, in some cases, invasion into the surrounding structure [6, 15, 16]. The size of the adrenal lesion directly relates to the potential malignant nature. If the mass size is greater than 4 cm, the sensitivity and specificity are 97% and 52%. If the size is greater than 6 cm, the sensitivity is 91%; specificity is 80% for the lesion to be adrenocortical carcinoma rather than adenoma [17]. In an unenhanced CT, the calculation of tissue density, which denotes the intracellular lipid content by measuring Hounsfield units (HU), is also helpful in distinguishing adenoma from ACC [11]. Usually, HU threshold of $\leqslant 10$ indicates a benign lesion, and a HU of >10 is suggested to indicate malignancy. But the difference between benign and malignant adrenocortical tumors based on imaging is not always straightforward. 13 HU is the cutoff for differentiating adenoma from carcinoma [18]. Another way is to get the contrast-enhanced CT scan, washout time [6, 11]. Although this approach has limitations, the adenomas have complete washout >50% compared to ACC, which retains the contrast longer. The MRI sensitivity is the same as CT differentiating adrenal adenomas from carcinomas. The sensitivity and specificity ranged from 84% to 100% and 92% to 100%. MRI feature which is specific to ACC includes isointense to hypointense signals on T1-weighted images and a heterogeneous signal drop on chemical shift [19, 20].

FDG-PET CT is a useful investigation for indeterminate cases on CECT scans. This is also useful to exclude distance metastasis. PET/CT may be used instead of CT in patients with impaired renal function. A combination of PET with CECT (FDG-CECT) can be considered a baseline assessment in an operable case of ACC. This can also help assess the response of palliative chemotherapy in metastatic cases [21, 22].

Newer tracers are also being tried in ACC cases. C-etomidate PET and (123) I-iodometomidate SPECT imaging are one of them. These tracers help distinguish between adrenocortical and nonadrenocortical lesions also metastases from adrenocortical carcinoma [23].

5.3 Biopsy

If a biopsy is clinically indicated, it is advisable to rule out pheochromocytoma biochemically to rule out the possibility of a fatal catecholamine surge during the procedure [24, 25]. Few studies show that biopsy increases the risk of morbidity and mortality [26, 27]. The decision on the need for adjuvant therapy should not be based on previous biopsy status and has not shown any relation to survival [28].

5.4 Pathology

Most ACCs are heterogeneous tumors with the invasion of the tumor capsule and associated nearby vital structures. The color of the resected mass varies from brown to yellow as per the lipid content inthe tumor tissues [6]. Histopathologically, it is tough to differentiate between adrenocortical tumors from carcinomas [29]. Weiss scoring system is one of the ways to determine the ACC from adrenal adenoma by looking into microscopic features on histopathology. This Weiss scoring system combines the nine morphological features, including nuclear atypia, mitotic index, atypical mitoses, diffuse architecture, confluent necrosis, clear cells, sinusoidal, venous, capsular (Table 1). Weiss score of 3 or more indicates an ACC, and 0 to 2 suggests an adenoma [30, 31].

The Ki-67 is a marker of proliferation (Ki-67 LI) and has shown a good correlation with survival. KI-67 value greater than 10% has shorter overall survival (OS) and more risks of local recurrences [32]. This also correlates with the Weiss criteria in predicting the aggressiveness of the tumors and is commonly reported by pathologists [33].

Table 1 Weiss Scoring System

Histological criteria	Score 0	Score 1
Nuclear grade[a]	1 and 2	3 and 4
Mitoses	≤ 5 for 50 fields × 400	≤ 6 for 50 areas × 400
Atypical mitoses	No	Yes
Clear cells	>25%	≤ 25%
Diffuse architecture	≤ 33% surface	> 33%
Confluent necrosis	No	Yes
Venous invasion	No	Yes
Sinusoidal invasion	No	Yes
Capsular infiltration	No	Yes

[a] Grade 1: (round nuclei, homogenous, small size, no nucleoli); Grade 2: (nuclei slightly irregular, more voluminous, conspicuous nucleoli at × 400); Grade 3: (unstable nuclei, voluminous nucleoli at × 100); Grade 4: (the same as Grade 3 with monstrous cells and very irregular nuclei)

Table 2 TNM classification system, proposed by ENSAT. T1, <5 cm; T2, >5 cm; T3

Stage	Characteristics		
I		T1, N0, M0	
II		T2, N0, M0	
III	T1-T2, N1, M0 T3-T4, N0-N1, M0		
IV	Any T, any N, M1		

6 ACC Staging

The most common staging system that is used for staging is ENSAT (European Network for the Study of Adrenal Tumors), which consists of the tumor, lymph node, and metastasis classification system that takes account of local extension of the primary tumor, lymph node involvement, and the presence of distant metastasis (Table 2). The Weiss system and TNM staging have an excellent concordance in predicting the prognosis of ACCs. TNM Stages III and IV patients usually have a high Weiss score [34]. The main difference between the ENSAT staging system and AJCC tumor-node-metastasis (TNM) classification is in stage III disease which in ENSAT includes patients with positive lymph nodes (N1), infiltration of surrounding tissues (T3 and T4), and venous tumor thrombus.

7 Management Principles

Management entails proper diagnosis and staging. Appropriate and sufficient investigations are required. It should ideally be a multidisciplinary team (MDT) effort. If the stage is possible, surgery to altogether remove the disease would be the first option. Adjuvant therapies, salvage therapies, and the treatment of metastatic disease are all difficult to administer and may not produce the desired results. They are used sparingly, as prescribed by MDT.

8 Surgical Management

Surgery is the only curative treatment in the case of operable ACCs, followed by adjuvant therapy in selected patients. Surgery can be done either by open adrenalectomy (OA) or minimally invasive surgery (Fig. 3). Staging the disease is essential before planning the surgery. This helps get information on the invasion of adjacent organs and distant metastases present in one-third of patients, mainly in the lung and liver [10]. A retrospective study of 201 patients underwent adrenalectomy for primary ACC (47 minimally invasive and 154 open surgery). All the postoperative histopathological parameters, post-op morbidity, and complications are similar; hence, in an experienced hand and adequately selected patient, minimally invasive surgery is a safe alternative to open surgery [35]. A recent metanalysis of nine retrospective case–control studies concluded no difference in overall recurrence rate or time to recurrence, or cancer-specific mortality between open and laparoscopic adrenalectomy. Laparoscopic adrenalectomy can result in a shorter hospital stay and faster recovery. Rarely laparoscopic approach was associated with a higher risk of peritoneal carcinomatosis because of the possible tumor capsule rupture during manipulation [36]. Complete surgical resection is the most crucial factor in the management of ACCs, and approximately two-thirds to three-quarters of ACCs have lymph node involvement [37, 38]. The role of routine lymphadenectomy during ACC surgical resection is still debatable, and its therapeutic role has not been proven, well-established predictor of poor long-term outcomes, however. In a multi-institutional study of 120 ACC patients undergoing complete resection, peritumoral lymph node dissection (performed in 27% of ACC patients) was independently associated with improved OS. It was also associated with large tumors macroscopically involved lymph nodes or invasion of adjacent organs [39]. In another review of the German ACC registry, lymphadenectomy was associated with improved disease-specific survival [40]. In contrast, in an extensive population study, data from 18 registries having 1525patients with ACC has not shown any survival benefit of lymphadenectomy. Lymphadenectomy is generally recommended in patients with locally advanced tumors (T3 and T4), which have more probability of lymph nodal involvement [41]. Debulking surgery of primary lesion in a metastatic condition has shown good palliative benefits. The removal of cancer also reduces the source of excess hormone in a secretory tumor without any significant improvement in median survival [11]. In patients with limited lung and liver metastasis at diagnosis, removal of primary and metastasectomy to achieve R0 resection has shown better long-term survival [42, 43]. Patients with ACC, who underwent curative surgery, have a high probability of recurrence, especially in higher stage patients, and can be seen in 40–65% of cases within 2 years. The average median time to recurrence is 19 months [44]. Patients presenting with limited recurrence and are amenable to curative-intent resection may be offered surgery as this approach is associated with improved long-term survival. Factors related to enhanced survival include solitary tumor, disease-free interval > 12 months, and locoregional or pulmonary recurrence [45].

9 Medical Management

9.1 Mitotane

This can be used as adjuvant or palliative therapy for the symptomatic benefit or combined with chemotherapy in the palliative setting [5]. There is no uniform consensus regarding the use of mitotane as adjuvant therapy. As per the ESMO guidelines, mitotane can be considered in Stage III, Ki-67 > 10%, microscopic margin positive, or gross positive resection [46].

With mitotane level monitoring, adjuvant mitotane is preferably started within 3 months of surgery. The intended level is to keep the mitotane between 14 and 20 mg/L. In a retrospective analysis, blood mitotane concentrations of more than 14 mg/L were associated with more prolonged recurrence-free survival [47]. Significant side effects include nausea, vomiting, raised liver enzymes, low WBC count, confusion, and other neuropsychiatric symptoms [48].

9.2 Chemotherapy

FIRM-ACT trial was a randomized phase 3 study of the combination of etoposide, doxorubicin, and cisplatin (M-EDP) with mitotane versus a combination of streptozocin with mitotane. Patients who received M-EDP had a higher response rate than those who received streptozocin plus mitotane (23.2% vs. 9.2%) and longer median progression-free survival (5.0 months vs. 2.1 months); however, there was no significant difference in overall survival (14.8 months and 12.0 months, respectively; hazard ratio, 0.79; 95% CI, 0.61 to 1.02; $P = 0.07$) [49].

For patients who had progressive disease on first-line treatment with M-EDP, chemotherapy with a combination of gemcitabine and capecitabine as a second-line therapy is an option. This combination regimen resulted in a nonprogressive disease in 46.3% of patients at the end of 4 months of treatment [50, 51].

9.3 Targeted Therapy

Various newer targeted therapies and monoclonal antibodies, such as bevacizumab, sorafenib, gefitinib, erlotinib, sunitinib, and axitinib, have not shown any encouraging results. Other newer targeted agents against steroidogenic factor-1, mTOR, and Wnt signaling pathways are under the process of development. Of these inhibitors, particular interest is on target acting against acetyl-CoA cholesterol acetyltransferase 1, an enzyme involved in intracellular cholesterol transport, is underway. It has shown promising activity in preclinical studies. Many phase I and II studies are ongoing for these novel agents and may be helpful for clinical applications in the future [52].

9.4 Radiation Therapy in the Management of ACC

The role of adjuvant radiotherapy (AR) in ACC is still evolving due to the lack of any randomized phase III studies. Various retrospective case series have shown benefits in local recurrence-free survival without affecting the disease free or overall survival. In a retrospective study from the German ACC cohort, the local recurrence 5 years after surgery was 79% in no adjuvant RT versus 12% in the adjuvant RT cohort without affecting the disease-free and overall survival [53, 54]. Another study by Habara et al. found no difference in the 5-year local recurrence-free rate between AR surgery and surgery alone (5 years local recurrence-free rate 53% (32–87%) in the RT group and 67% (52–86%) in the non-RT group ($P = 0.53$) [55]. Sabol et al. compared the non-radiotherapy treatment regimens with adjuvant RT. The use of adjuvant RT was associated with a 4.7-fold decrease in the risk of local recurrence [56]. Although the data for the benefit of adjuvant RT is not robust, with the available literature, adjuvant radiotherapy is strongly recommended in patients who have an incomplete resection, those with positive margin resection, and all those patients at high risk of local recurrence [11].

Stereotactic body radiotherapy (SBRT), which aims at delivering high-dose radiation, is an option for minor, localized recurrence and also for palliative therapy in a subset of patients with advanced adrenocortical carcinoma [57].

10 Algorithms for Stage-Wise Management (Fig. 4)

11 Prognosis by Stage with Current Treatment (Table 3)

Table 3 Stage-wise prognosis

Stage	5-year survival
I	33–66%
II	20–58%
III	18–24%
IV	<5%

12 Palliative Measures

In patients presenting with metastatic disease, no curative option is available. Treatment aims for the symptomatic benefit primarily associated with the excess catecholamine secretion and local and metastatic disease spread. Treatment options include locoregional therapies, systemic chemotherapy, and radiopharmaceutical agents [58]. The treatment plan should be preferably discussed with a multidisciplinary team. Some patients benefit from local embolization and radiofrequency ablation, even in metastatic settings.

Radionuclide therapy with 131I MIBG is effective in selected cases. There are few studies on the efficacy of 131I-MIBG treatment in the palliative setting. Responses rates were ranged from 22% to 47%, with few long-term control lasting for 4 years. More objective responses were seen in patients having soft tissue metastases [59, 60].

How We Do It at TMC

- Detailed history, examination, vitals.
- Specific blood tests—for an adrenal mass glucocorticoids, mineralocorticoids, sex.
- Steroids and catecholamine levels.
- Imaging as required—CT scan/MRI/FDG PET CT scan.
- Endocrinology reference/evaluation.
- MDT discussion.
- Treatment as decided in MDT tumor board.
- Post therapy MDT discussion and follow-up/adjuvant or additional therapy.

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Urinary Bladder Cancer

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Abbreviations

CIS	Carcinoma in situ
CMV	Cisplatin, methotrexate, vinblastine
DCE	Dynamic contrast enhanced
DNA	Deoxyribonucleic acid
DSS	Disease-specific survival
FDG	18F-fluorodeoxyglucose
GC	Gemcitabine and cisplatin
IGRT	Image guided radiotherapy
IMRT	Intensity-modulated radiation therapy
MIBC	Muscle-invasive bladder cancer
MMC	Mitomycin C
M-VAC	Methotrexate, vinblastine, doxorubicin and cisplatin
NBI	Narrow-band imaging
NMIBC	Non-muscular invasive bladder cancer
PTV	Planning target volumes
RNA	Ribonucleic acid
TNM	Tumour, node, metastasis
TURBT	Transurethral resection of bladder tumor

1 Introduction

Bladder cancer is the most common malignancy of the urinary system and the ninth most common malignancy worldwide [1]. Carcinoma of the bladder can present as a superficial disease or locally advanced muscle-invasive or metastatic disease. This heterogenous presentation warrants different management strategies and has different survival outcomes.

2 Incidence

As per GLOBOCAN 2018, the age-standardized incidence rate in US and India is 12 and 1.5 (per 100,000 population) respectively [2]. It is the fourth most common cancer in men and the eighth most common malignancy in women in the Western world [3]. In the United States, approximately 81,000 new cases and 17,000 deaths occur each year due to bladder cancer [4]. There has been an increase in the age-standardized incidence rate by 13·6% (95% CI - 1·0 to 22·0)) from 1990 to 2016 in India [5]. In males, the genitourinary system formed 17.48% of all the malignancies (urinary bladder [30.40%]) [6].

Bladder cancer is typically diagnosed in older individuals, with a median age at diagnosis of 69 years [7], and has a male preponderance (86.4% male vs. 13.6% female) [8].

3 Epidemiology

Cigarette smoke: the most important factor [9]. Heavy smokers (≥ 30 pack years) are more prone to advanced-stage disease or high-grade tumor [10]. Smoking cessation decreases the risk.

Chemicals: paint components, polycyclic aromatic hydrocarbons such as 2-naphthylamine, benzidine, and diesel exhausts, cyclophosphamide administration over the long term.

Chronic irritants: including catheters, recurrent urinary tract infections, Schistosoma haematobium, and irradiation (for squamous carcinoma).

Genetic abnormalities: 17p deletion, p53 expression, RB gene expression, 9q aberration.

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Table 1 Clinical presentation [12–14]

Clinical presentation	Incidence of bladder cancer
Gross painless hematuria (80–90%)	10–20%
Microscopic hematuria	2–5%
Irritative voiding symptoms (dysuria, urgency, frequency) 20–30%	Indicates CIS
Pain: • Flank pain: associated with muscle-invasive disease or large non-invasive tumors at the ureteral orifice • Suprapubic pain: involvement of perivesical tissue or nerves/bladder outlet obstruction • Perineal pain: involvement of obturator fossa, perirectal fat, presacral nerves, or the urogenital diaphragm. • Right upper quadrant upper abdominal pain: presence of abdominal lymph node or liver metastases. • Bone pain: the presence of bone metastasis • Persistent headache or disordered cognitive function: presence of intracranial or leptomeningeal metastases	–

4 Clinical Presentation in India and Globally

At presentation, 1/third are muscle-invasive tumors, of which 5–10% are metastatic [11]. Painless hematuria is the most common presentation with irritative voiding symptoms present in only one-third of patients. (Table 1) [12–14].

Locally advanced tumors usually present with painful obstructive symptoms due to ureteric orifice involvement and sometimes with constitutional symptoms of renal failure due to bilateral ureteral obstruction. Failure to thrive, weight loss, fatigue, and anorexia are the usual mode of presentation in metastatic patients indicating poor prognosis.

Episodic hematuria presentation in middle-aged smokers or those with exposure to industrial carcinogens needs a word of caution and should be thoroughly investigated for bladder carcinoma. Urine cytology, cystoscopy, and imaging (CECT-IVU) are suggested.

5 Investigations

The important objectives of investigation in bladder cancer are diagnosing the presence or absence of muscle invasion and staging the patients appropriately for optimum care.

Urine Cytology:

In high-grade tumors or carcinoma in situ (CIS), the sensitivity of freshly voided urine cytology samples is high (~90%) even with unequivocal imaging findings indicating lesions anywhere in the urinary tract. Since the overall sensitivity of urine cytology examination is low (sensitivity: 40–60%, specificity: 90%), negative cytology does not exclude the presence of low-grade bladder tumor [15].

Table 2 Urinary biomarkers for diagnosing urothelial cancers of the bladder [16, 18, 19]

Target	Sensitivity (%)	Specificity (%)	False positives
Bladder tumor antigen (BTA)	50–90	90	Urinary tract infection, hematuria, calculi, BPH, prior intravesical treatment
Nuclear matrix protein (NMP 22)	42–100	70–91	Inflammation
NMP 52	97	94	–
Bladder cancer associated NMP 4 (BCLA −4)	89–96	95–100	–
BCLA-1	80	87	–
Survivin	64–100	93–100	–
Cytokeratin 8 and 18	35–79	68	–
CK 19	43–96	70	Urinary tract infection, calculi, post-BCG
Fibrin degradation products (FDP)	70	68–86	–
Hyaluronic acid, hyaluronidase	82–100	81–90	–
mRNA markers (IGFBP5, HOXA13, MDK, CDK1, CXCR2	74–95	45–81	–

6 Tumor Markers

Tumor markers are considered as a non-invasive diagnostic tool to supplement cystoscopy (pooled sensitivity of 50–80% and specificity of 70–90%) due to the low sensitivity of urine cytology examination [16, 17]. It correlates closely with the stage and grade of the tumor. Multiple urine-based tumor markers were developed based on differential expression of tumor-related proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or cellular markers (Table 2) [16, 18, 19].

Potential applications of urinary biomarkers:

1. Presence of hematuria and irritative voiding symptoms, atypical findings on cytology or cystoscopy, as they are at high risk of tumor diagnosis.
2. Surveillance: Treated non-muscle invasive tumors to detect recurrences.
3. Evaluation of upper tract radiographic abnormalities and monitoring patients after treatment of ureteral or renal pelvic urothelial carcinoma.
4. Predicting outcomes for patients being treated with intravesical immunotherapy, but this awaits validation [20].

Limitations:

Unnecessary imaging and bladder biopsies are the drawbacks associated with its higher false positive rates.

Since the cost-effectiveness and incremental benefit of markers are unknown, additional clinical trials are necessary.

7 Endoscopy

The gold standard for diagnosis of bladder cancer. (Fig. 1).

1. The presence of a palpable mass on bimanual examination under anesthesia implies an extravesical disease or fixity to pelvic side walls, which helps in the local staging of tumors especially invasive tumors.
2. Cystoscopy helps in visualizing the size, stalk, and configuration of the cancer, which can be the predictive factor of muscle invasion [21]. Papillary tumor with narrow stalk indicates low-grade non-invasive malignancy, whereas sessile tumour with solid or nodular pattern is seen more frequently in high-grade malignancies. Carcinoma in situ are exceptions, as they are high-grade but non-invasive and appear as flat velvety lesions in patches, sometimes can involve large areas of the urothelial lining.

7.1 Principles of Cystoscopy + TURBT

1. Any visible tumor or suspicious lesion seen at the initial (diagnostic) cystoscopy should be either biopsied or transurethrally resected down to the muscle. Superficial and deep tissue should always be sent separately to determine the histology and depth of invasion by oncopathologist. (Table 3) [15].
2. Positive urine cytology with negative cystoscopy examination findings require a biopsy of apparently normal-appearing urothelium, prostatic urethra, and selective catheterization of the ureters/renal pelvis to retrieve urine specimens for cytology from the upper tract.

There is no role for random biopsies in a patient with a solitary papillary lesion as the incidence of CIS is less than 2% and the risk of accidental tumor cell implantation with no additional information.

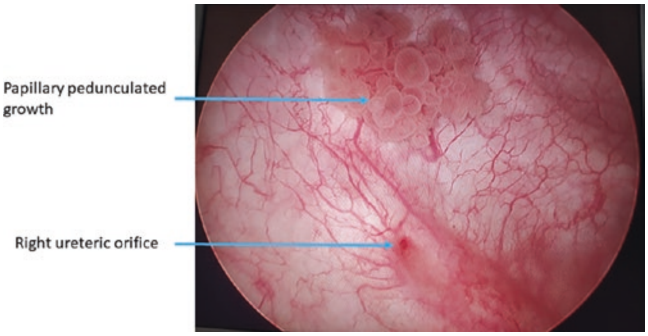


Fig. 1 Cystoscopy image showing papillary pedunculated growth above right ureteric orifice suggestive of urothelial bladder cancer

7.2 Enhanced Cystoscopy

Fluorescence cystoscopy (PDD) or narrow-band imaging (NBI) are emerging new technologies focussing on improved detection of small or flat lesions. NBI is less well studied, thus guidelines statements focus on PDD [22].

7.3 Fluorescence Cystoscopy (Blue Light Cystoscopy)

Fluorescence cystoscopy detects more tumors (both papillary and CIS) than white-light cystoscopy, which has been confirmed by various randomized trials thus improving the tumor identification rate and resulting in better patient management (Table 4) [22].

Enhanced cystoscopy at the times of TUR has been recommended by both AUA and NICE guidelines.

EAU recommends PDD-guided biopsies in the setting of positive cytology but negative cystoscopy.

NCCN does not recommend routine use of PDD-enhanced cystoscopy, citing a lack of evidence regarding reduced progression.

7.4 Narrow Band Imaging

Narrow band imaging is an optical enhancement technology that narrows the bandwidth of the light into 415 and 540 nm and thereby increases the visibility of microvascular structures in the mucosal surface, which are abundant in urothelial tumors.

7.5 Microscopic Imaging Techniques

Optical coherence tomography and confocal laser endomicroscopy provide high-resolution cross-sectional views of vesicular tissues which resemble images obtained for

Table 3 Indication of prostatic urethral biopsies [15]

1. Bladder neck tumor
2. Bladder CIS is present or suspected
3. Positive cytology without evidence of tumor in the bladder
4. Abnormalities of the prostatic urethra are visible

Table 4 Advantages of PDD (blue light cystoscopy) [22]

1	Improve detection rate (particularly CIS)
2	Urinary cytology persistently positive without any demonstrable bladder lesion
3	Reduce residual disease after TUR
4	Decrease recurrences
5	Possibly decrease progression

Table 5 Disadvantages of enhanced cystoscopy

1. Inflammation and scarring lead to a higher false positive rate.
2. Requirement of the special lens system
3. Need to instill the photosensitizer 1 h prior to cystoscopy
4. Rigid rather than flexible cystoscopy
5. Higher cost

histopathological examination. Therefore, these are referred to as "optical biopsy".

7.6 Molecular Imaging

Molecular imaging combines optical imaging with fluorescent labeling of elements such as antibodies offering highly specific real-time visualization of cancer cells and their differentiation from healthy tissue.

The disadvantages and limitations of enhanced cystoscopy are enumerated in Table 5.

8 Radiology

Imaging is an essential component to complete the staging, so as to know the extent of local tumor invasion, and nodal and distant metastasis, and also helps in prognosticating the patients.

8.1 Ultrasonography of the Abdomen and Pelvis

It is considered the first investigating modality to assess the anatomical location and also know the status of the entire urothelial tract. However, it has been replaced by cross-sectional imaging (CT or MRI) for most patients today [23].

8.2 CECT Urography

CT Urography (CTU) should include both the abdomen and pelvis and delayed images to identify defects in the collecting system and is now considered the gold standard for evaluation of patients with initial hematuria presentation (Fig. 2). CT scan is approximately 80 percent accurate in differentiating locally advanced tumors involving extravesical adipose tissue or surrounding structures from less invasive tumors [24]. The role of CTU is limited after TURBT, as it is difficult to distinguish inflammatory or iatrogenic oedematous changes from true extravesical tumor extension.

8.3 MRI for Local Staging of Invasive Bladder Cancer

It has superior soft tissue contrast resolution but poorer spatial resolution compared with CT scans and is considered 73–96% accurate in primary tumor staging. Dynamic contrast-enhanced (DCE) MRI helps in better evaluation of post-biopsy resection cases. VIRADS scoring system has been suggested to evaluate local invasion of bladder tumors. An ongoing randomized trial (BladderPath) is assessing if MRI can reliably predict muscle invasion and obviate the need for doing a TURBT [25].

8.4 Comparison of CT and MRI for Local Staging

The aim of CT and MRI scanning is to detect T3b disease or higher. The perivesical extension is better appreciated on MRI and is recommended for the same. Abdominal nodes >10 mm and pelvic nodes >8 mm in maximum short-axis diameter should be regarded as enlarged on CT and MRI scans. For optimal staging, either MRI with fast dynamic contrast-enhancement or MDCT with contrast enhancement is recommended [26].

8.5 Metastatic Work-Up

Chest radiographs are performed to rule out pulmonary metastases; however, a CT scan is the most sensitive means of detecting pulmonary metastasis.

An isotope bone scan is done to detect bony metastasis and is also useful as a baseline for future reference, particularly in patients with bone pains or increased alkaline phosphatase.

To exclude brain metastasis CT or MRI of the brain should be done if clinically indicated.

8.6 Role of PET-CT Scan in Metastatic Work-Up

PET has limited value and does not yet have an established role in patients with localized bladder cancer due to urinary excretion of 18F-fluorodeoxyglucose (FDG) [27].

Preoperatively, PET/CT is a promising tool to detect metastatic disease, especially in a high-risk disease where the CT or MRI remained inconclusive on distant metastases or in locally advanced bladder carcinoma patients. In a study of 55 patients with bladder cancer, integrated PET/CT improved the preoperative tumor, node, metastasis (TNM) staging compared with CT alone in 15 percent of patients [28].

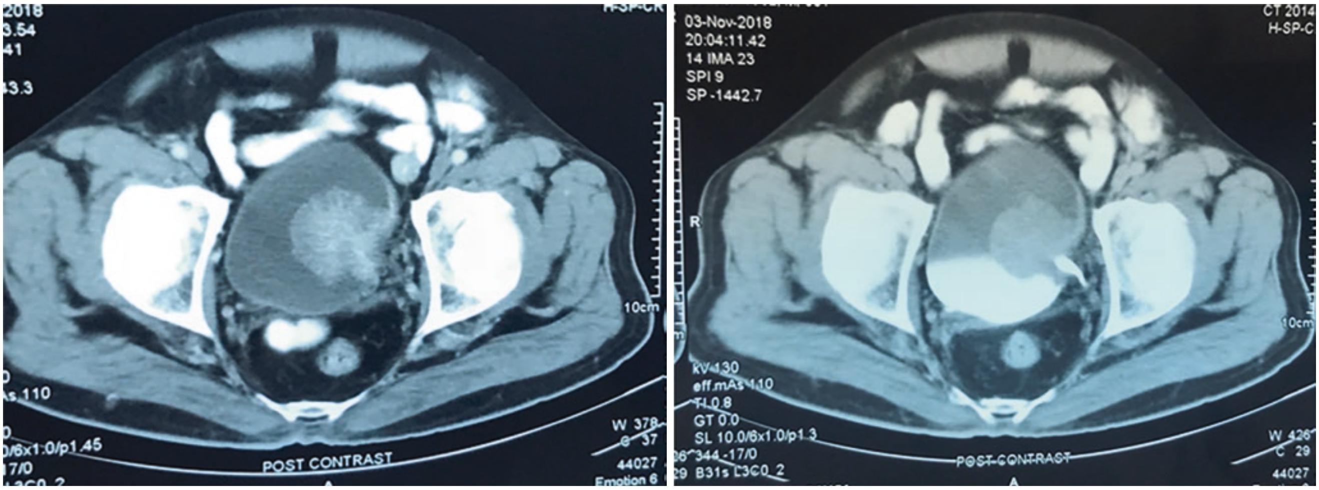


Fig. 2 CECT (IVU) showing large proliferative growth in the left lateral wall with involvement of the left vesico-ureteric junction

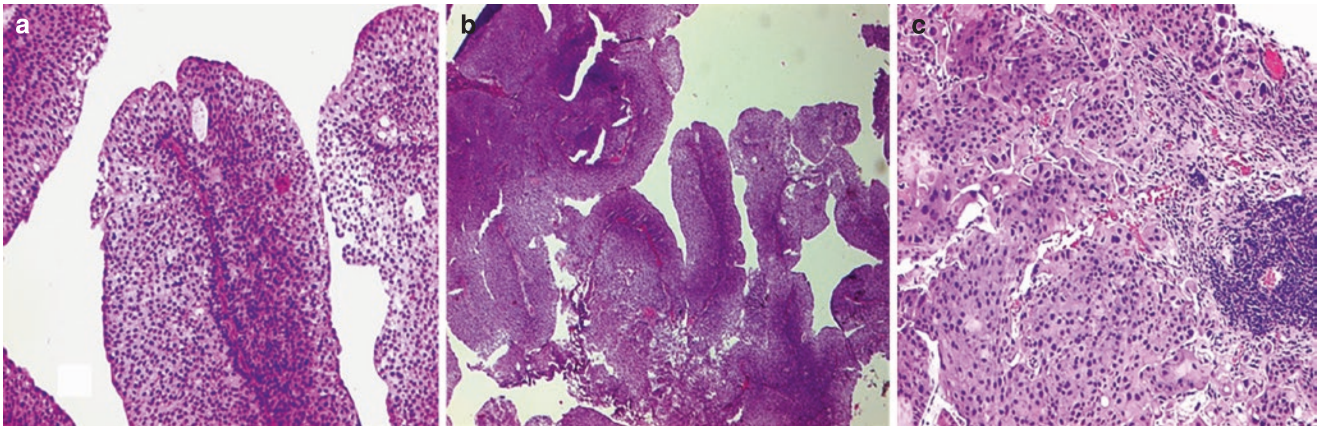


Fig. 3 (**a**, **b**) Microphotograph showing low-grade transitional cell carcinoma. (**c**) High-grade transitional cell carcinoma

9 Pathology

Bladder cancer is a field change and is notorious for multiple recurrences often at new sites. Morphologically a majority (70%) are exophytic papillary tumor confined to mucosa (Ta) or invade submucosa (T1). About 50–70% of NMIBC tumors recur and 5–20% of them progress to invasive disease. Histopathologically, the majority of bladder cancers are urothelial carcinoma (90–95%). Low-grade tumors (G1) have a high local recurrence rate but progression to muscle-invasive disease is low. High-grade NMIBC tumors have a high propensity to transform into invasive tumors which are considered high-grade histologically. (Fig. 3).

Various histological variants exist that are missed on initial transurethral resection specimens (Table 6) [29–31]. Study results showed that analysis of transurethral resection specimens revealed only 39% of cases of histological variants later confirmed at radical cystectomy, and up to 44% of cases of histological variants were not recognized or documented by community pathologists [20].

Table 6 Other histological variants [29–31]

	Histological variants	Incidence (%)
1	Urothelial with squamous differentiation	60
2	Urothelial with glandular differentiation	06
3	Pure squamous cell tumor with keratinization (Schistosomia infestation and chronic irritation)	03
4	Adenocarcinoma (embryonal remnants of urachus)	02
5	Urothelial carcinoma (micro-papillary variant)	0.7–2.2
6	Urothelial carcinoma (nested variant)	–
7	Urothelial carcinoma (plasmacytoid variant)	–
8	Small cell variant	–

9.1 Histological Grading

All available tumor classification still has inherent limitations. The WHO 1973 classification showed Grade 2 tumor had variable presentation between G1/G2 and G2/G3. So, WHO 2004 classification introduced the concept of low-grade and high-grade urothelial carcinoma, which has been

Table 7 Histological grading of bladder urothelial carcinoma [20, 32, 33]

1973 WHO grading urothelial papilloma
• Grade 1: Well differentiated
• Grade 2: Moderately differentiated
• Grade 3: Poorly differentiated
2004/16 WHO ISUP grading
• Papillary urothelial neoplasm of low malignant potential (PUNLMP)
• Low-grade papillary urothelial carcinoma
• High-grade papillary urothelial carcinoma

retained in the WHO 2016 classification also. The WHO 1973 and 2004 classifications have been compared in Table 7 [20, 32, 33]. Staging can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 763–764, Chapter no.62, Urinary Bladder, Table: Definition of TNM and which can be accessed at https://emedicine.medscape.com/article/2006834-overview [34].

10 Genetic Counselling

Bladder cancer is typically not inherited. Most often, tumors result from genetic mutations that occur in bladder cells during a person's lifetime. These non-inherited genetic changes are called somatic mutations.

Spanish bladder cancer study showed that a family history of cancer in first-degree relatives was associated with an increased risk of bladder cancer and showed a stronger association amongst younger patients.

Based only on epidemiological and clinicopathological variables, the important goal of identifying genetic susceptibility loci for cancer risk and outcome is to incorporate them into a comprehensive risk prediction model to improve prediction over currently available models [35].

11 Principles of Management

- Non-muscular invasive bladder cancer (NMIBC) has replaced superficial bladder cancer terminology.
- Properly performed and complete initial transurethral resection of all visible bladder tumours is essential, and an early repeat resection should be performed when indicated.
- Perioperative intravesical chemotherapy decreases recurrence rates by 13%.
- Patients should be risk stratified according to pathology, clinical history, and response to intravesical therapy.
- According to risk stratification, patients should be offered expectant management, intravesical therapy, or radical cystectomy, as appropriate.
- The definitive therapy for muscle-invasive bladder cancer (MIBC) is radical cystectomy or radiation therapy (trimodality) to the bladder.
- A standard template pelvic lymphadenectomy includes the genitofemoral nerves laterally, the internal iliac artery medially, the Cooper ligament inferiorly, and the point at which the ureter crosses the common iliac artery superiorly.
- Based on prospective clinical studies, neoadjuvant cisplatin-based chemotherapy has shown a benefit of 5–10% absolute improvement in 5-year overall survival.
- Patients who did not receive neoadjuvant chemotherapy but have high-risk disease (defined as T3, T4 disease, or presence of nodal metastasis) after radical cystectomy should be considered for adjuvant cisplatin-based chemotherapy.
- Partial cystectomy can be considered in rare, solitary urothelial tumors without concomitant CIS.
- Urachal adenocarcinomas are treated with en-bloc resection of the umbilicus and dome of the bladder.
- The follow-up of non-muscle invasive bladder cancer is based on the principles of regular cystoscopy and urine cytology due to the risk of recurrence and progression.

12 Surgical Management

12.1 Management of Non-muscle Invasive Bladder Cancer

Transurethral resection of bladder tumor (TURBT): Transurethral resection of the bladder tumor(s) is the standard of care for staging bladder tumors and as a part of curative treatment especially in Ta/T1 tumors on pathology. In very small tumors (less than 1 cm) en bloc resection with the underlying bladder wall is the key, whereas larger tumors should be resected in superficial and deep fractions to know the invasiveness of the tumor.

During resection, cauterization of tissue should be avoided to prevent its destruction.

Re-TURBT (Table 8) [22]: Accurate staging of disease is important for optimum treatment and under-staging may lead to inadequate treatment and poor outcomes. Since 33–53% of the patients have residual disease on second resection indicating a significant risk of under-staging in TaT1 tumors and 20% upstaged to the invasive tumor, so second TURBT has shown to increase recurrence-free and progression-free survival. Though there is no consensus regarding the timing of the second TUR, it is generally recommended 2 to 6 weeks after the initial TURBT and should always include resection of the primary tumor site [15, 22].

EORTC after studying the database of 2500 patients developed a scoring system and risk tables to predict the risk

Table 8 Recommendations for the performance of Re-TUR [22]

1	Incomplete initial resection
2	High-risk (recurrent, multifocal, >3 cm)
3	HG pTa tumor (high-grade tumor)
4	Any T1 tumor—resection to include detrusor muscle
5	Detrusor muscle not sampled in the initial specimen—except tag1 and primary CIS or
6	Presence of LVI

Table 9 Prognostic factors for recurrence and progression [22]

High-grade or poorly differentiated tumors (G3)
Co-existent CIS or dysplasia in random mucosal biopsies
Multiple or multicentric tumors
Multiple recurrences within a short period of time (rapidly recurrent tumors)
Lamina propria invasion (T1)
Tumor size of more than 3 cm
Prostatic urethral involvement

of recurrence and progression separately in individual patients.

Table 9 enumerates the factors governing recurrence and progression. Despite an adequate transurethral resection, nearly 70–80% of patients will have a relapse within the bladder while 20–25% will progress to muscle invasion.

Based on tumor grade, size, number, and prior recurrences, NMIBC is risk-stratified (Table 10). Bladder cancer with a low risk of recurrence or progression can be managed by close surveillance and regular check cystoscopy, while those with a high risk of relapse need intravesical chemotherapy or immunoprophylaxis. Table 11 mentions the recommendation for intravesical therapy based on risk stratification.

12.2 Single Post TURBT Instillation

A single immediate post-operative instillation of chemotherapy is recommended in all patients irrespective of the risk group, provided there is no perforation or bleeding.

Timing of the instillation is crucial and is recommended within 24 h (preferably within 6 h).

Meta-analysis of seven RCTs supports the use of single post-operative instillation as recurrence rates are decreased by 12%.

As the recurrence rate is very low after single instillation immediately after TURBT in low-risk group papillary tumors, no further treatment is advised. Intermediate- and high-risk patients require a further 4–8 weeks course of intravesical therapy.

Mitomycin C (MMC), epirubicin, and doxorubicin have all shown comparable beneficial effects. Table 12 [36] enumerates the principles for perioperative intravesical therapy.

Table 10 Risk stratification for non-muscle invasive bladder cancer [22]

Low risk	Intermediate risk	High risk	Highest risk subgroup
PUNLMP	Solitary low-grade Ta > 3 cm	High-grade T1	T1G3/HG associated with concurrent bladder CIS
Low-grade solitary Ta </= 3 cm	Multifocal low-grade Ta	Recurrent high-grade Ta	Multiple and/or largeT1G3/HG
No CIS	Recurrence within 1 year of low-grade Ta	High-grade Ta > 3 cm	Recurrent T1G3/HG
–	All tumors not categorized as low or high risk	Multifocal high-grade Ta	T1G3/HG with CIS in the prostatic urethra
–		Any CIS	Some forms of variant histology of urothelial carcinoma
–	–	Any BCG failure in high-grade cases	LVI positive
–	–	Any variant histology	–
–	–	Any LVI	–
–	–	Any high-grade prostatic urethral involvement	–

Table 11 Recommendations for intravesical therapy in non-muscle invasive bladder cancer [22]

All patients	Single-instillation of intravesical chemotherapy within 24 h of TUR (exception perforation or bleeding)
Low-intermediate-risk	Single instillation of intravesical chemotherapy post-TUR
Low-risk:	Do not offer induction chemotherapy
Intermediate-risk	Consider induction chemotherapy or immunotherapy Maintenance may be utilized in those that respond to induction chemotherapy Maintenance should be considered for 1 year in those that respond to induction BCG
High-risk	Administer induction BCG and continue maintenance BCG for 3 years, as tolerated
Tis	BCG induction with maintenance

12.3 Additional Adjuvant Intravesical Therapy

The need for further adjuvant chemotherapy or BCG immunotherapy largely depends on the risk of recurrence or progression (Table 13) [15, 37].

Table 12 Perioperative intravesical therapy to prevent tumor implantation [36]

Single-dose intravesical chemotherapy administered within 6 h of resection reduces recurrence of low-risk tumors, with significant impact in the setting of initial presentation of solitary low-grade papillary tumors
The incremental benefit in patients with recurrent or multiple tumors is limited
No benefit has been found in patients with high-grade disease

Table 13 Role of adjuvant intravesical BCG (immunotherapy) [15, 37]

1	Intravesical BCG has higher efficacy and side effects compared to intravesical chemotherapy
2	BCG is the only agent shown to delay or reduce high-grade tumor progression reduces the need for cystectomy, increase the time to cystectomy, and improve survival
3	For intermediate and high-risk diseases, maintenance BCG is advised to achieve the best results, provided patients can tolerate it
4	The meta-analysis concluded that at least 1 year of maintenance BCG was required to show the superiority of BCG over MMC in preventing recurrence or progression

A meta-analysis of the MRC and EORTC data comparing intravesical chemotherapy to TURBT alone demonstrated that chemotherapy prevents recurrence but not progression [38].

Four meta-analyses have confirmed the role of BCG after TURBT is superior to TURBT alone or TURBT and chemotherapy in preventing recurrences of TaT1 tumors.

The efficacy of intravesical chemotherapy in reducing the risk of recurrence was demonstrated in the primary as well as recurrent settings by 2 meta-analyses by Huntcharek in 2000 and 2001.

Since there is no optimum BCG schedule with optimal dose yet undefined based on high-level evidence, most centers follow the schedule described by Lamm. The EORTC meta-analysis of nearly 5000 patients demonstrated that there is a 27% reduction in the rate of progression after intravesical BCG treatment in both TaT1 and CIS disease. Weekly instillations for 6 weeks are a commonly used empirical schedule. To reduce BCG toxicity, several authors have proposed a dose reduction of BCG to one-third to one-fourth of the standard dose. The Spanish Oncology Group (CUETO) compared the standard dose with a one-third dose of BCG in a randomized trial and did not find any difference in efficacy, except in patients with high-risk prognostic groups [39, 40]. Table 14 enumerates the contraindications of intravesical BCG.

Table 14 Contraindications of intravesical BCG [38]

Absolute contraindications	Immunosuppressed and immunocompromised patients
	Personal history of BCG sepsis
	Gross hematuria (intravasation risk post TUR)
	Traumatic catheterization (intravasation risk post-TUR)
	Total incontinence
Relative contraindications	Urinary tract infections
	Liver disease
	Personal history of tuberculosis
	Advanced age
	Poor overall performance status

12.4 Recommended Strategies for Treatment of BCG Failure

BCG failures comprise refractory, relapsing, unresponsive disease and intolerant patients (Table 15). BCG toxicity is a common scenario in BCG failure cases. Radical cystectomy is considered the standard-of-care for these patients.

Salvage therapeutic strategies for BCG failures unfit or unwilling to undergo surgery comprise intravesical chemotherapy, chemoradiation, or chemohyperthermia.

Intravesical chemotherapy: Various agents used are valrubicin, gemcitabine, and intravesical taxanes (docetaxel, paclitaxel). Valrubicin is the only approved option for BCG-refractory patients with CIS if cystectomy cannot be performed. Gemcitabine and Docetaxel have been used as salvage mono chemotherapy agents with 1-year disease-free response rates varying from 21% to 50% in various series. Combination chemotherapy regimens like intravesical gemcitabine followed by intravesical docetaxel with 6 weekly induction and monthly maintenance for 2 years has 1- and 2-year response rates of 54% and 34%, respectively. Similar response rates were reported with a combination of intravesical gemcitabine with mitomycin C (MMC), but response rates significantly decline after 2 to 5 years [41].

Chemohyperthermia: It includes delivery of hyperthermic intravesical chemotherapy (HIVEC) with temperatures of 41 to 44 °C. The hypothesized mechanism is that there is a direct cytotoxic effect and hyperthermia enhances the penetration of chemotherapeutic agents into the bladder wall with hyperthermia. In NMIBC, chemohyperthermia is combined with the instillation of MMC, which displays greater toxicity under increased temperature, thereby enhancing its effects. Hyperthermia can be applied to the bladder with different modalities and different devices (Synergo, Combat,

Table 15 Classification of BCG failures [20]

Classification of BCG failures	Definition	Treatment
Adequate *BCG treatment	Patients receiving at least five of six planned instillations of induction treatment and at least two of three planned instillations of maintenance treatment over 6 months	–
BCG refractory	Persistent high-grade disease at 6 months after adequate BCG induction and maintenance treatment or any progression in stage at 3 months assessment (i.e. after induction BCG cycle	Radical cystectomy Bladder-preserving strategies in patients unsuitable for radical cystectomy
BCG relapsing 1. Early relapse: <12 months 2. Intermediate relapse: 12–24 months 3. Late relapse: >24 months	Recurrence of high-grade disease after a disease-free interval of > = 6 months after adequate BCG induction and maintenance treatment	Radical cystectomy Bladder-preserving strategies Repeat BCG course
BCG unresponsive	Included BCG relapsing and BCG refractory. BCG relapsing patients should have a recurrence within 6 months of the last BCG exposure. The highest risk of recurrence and progression	–
BCG intolerant	The disease is persistent because the patient cannot receive adequate BCG owing to BCG toxicity	Radical cystectomy is recommended Alternate intravesical therapy

Unithermia), among which the Synergo system is based on radiofrequency-induced hyperthermia, is the most frequently used. Reported recurrence-free rates for chemohyperthermia vary between 40% and 60% after 2 years; however, data on long-term outcomes are missing [41, 42].

Immune checkpoint blockade: The preliminary results of single-arm KEYNOTE-057 phase II trial (NCT02625961), in which the anti-PD-1 antibody pembrolizumab istested in patients unresponsive to BCG who are considered ineligible for or have refused to undergo radical cystectomy. After a median follow-up of 15.8 months, the complete response rate was 40.2%, with a median CR duration of 12.7 months. 36.6% of patients developed recurrent NMIBC after having a complete response and no patients progressed to muscle-invasive disease/metastatic disease. A phase 3 study evaluating pembrolizumab in high-risk non-muscle invasive bladder cancer that is persistent after BCG induction (KEYNOTE 676) is underway. Several trials are currently ongoing with anti-PD-L1 antibody atezolizumab, alone or in combination with BCG and nivolumab an IDO-1 inhibitor or BCG (CheckMate 9UT, NCT03519256), or durvalumab (NCT02901548) [43].

Table 16 Cleveland clinic approach for complications associated with intravesical BCG administration [45]

Grade 1: moderate symptoms < 48 h Mild or moderate irritative voiding symptoms, mild hematuria, fever <38.5 °C	Symptomatic management Anticholinergics, topical antispasmodics (phenazopyridine), analgesics, nonsteroidal anti-inflammatory drugs
Grade 2: severe symptoms and/or > 48 h Severe irritative voiding symptoms, hematuria, or symptoms lasting >48 h	Consider dose reduction to one-half to one-third of the dose when instillations resume Administer isoniazid and rifampicin, 300 mg/day and 600 mg/day, orally until symptom resolution
Grade 3: Serious complications (hemodynamic changes, persistent high-grade fever)	Isoniazid, 300 mg/day, and rifampicin, 600 mg/day, for 3–6 months depending on the response

Mycobacterium phlei cell wall nucleic acid complex (MCNA): It is an immunotherapeutic agent derived from M. phlei that has been used in BCG-refractory or BCG-relapsing patients. Recently, in a single-arm phase III trial with 129 BCG failure patients treated with induction and maintenance MCNA, recurrence-free survival rates of 25% after 12 months and 19% after 24 months were reported.

Viral gene therapies and targeted therapies are currently tested in several clinical trials in patients after BCG failure. Interim results are encouraging and selected approaches might be added to the physician's armamentarium for bladder-sparing options after BCG failure in the future [43, 44].

Table 16 classifies BCG toxicity and its management [45].

12.5 Cystectomy for Non-muscle Invasive Bladder Cancer

Despite intravesical adjuvant therapies, there is a substantial group of patients with initial high-grade stage T1 tumor who have progression and are at risk of dying from urothelial cancer. It is reasonable to propose immediate cystectomy to those patients who are at high risk of progression (multiple recurrent high-grade tumors, high-grade T1 tumors, high-grade tumors with concomitant CIS). Cystectomy is advocated in patients with BCG failure and delaying cystectomy in these patients may lead to decreased disease-specific survival [15].

12.6 Management of Carcinoma-In-Situ

Carcinoma in situ of the bladder may exist alone (primary CIS) or in combination with a bladder tumor. Primary CIS confined to the bladder is treated with intravesical BCG, with excellent complete response rates of 82–93%. Recurrence of primary CIS despite the first course of BCG may be treated with a second course of BCG with a response seen in 40–50% of patients. CIS associated with an overt tumor is treated according to the merits of the tumor. Approximately 50% of patients develop the recurrent disease with muscle invasion or extravesical tumor, and 10–20% die of their disease within 5 to 7 years after an initial complete response. Non-responders or incomplete responders have a significant risk of tumor progression and cystectomy is recommended in such patients. Patients with an incomplete response at 9 months, recurrent tumors, or extravesical disease also need cystectomy [15]. Table 17 classifies CIS as per clinical type [15, 46].

12.7 Follow-Up Schedules in NMIBC

Prompt detection of muscle-invasive and high-grade non-muscle-invasive recurrences is critical and delay in diagnosis and therapy could compromise survival. Tumor recurrence in a low-risk group is nearly always low-stage and low-grade and does not pose a threat to life. High-risk patients may present as muscle-invasive disease on recurrence and need immediate diagnosis and treatment. The result of the first cystoscopy after TUR at 3 months is an important prognostic factor for recurrence and progression and hence cystoscopy at 3 months post-TUR is recommended in all patients [22]. The follow-up protocol for NMIBC is summarized in Table 18.

12.8 Management of Muscle-Invasive Bladder Cancer

Newly diagnosed bladder cancers have muscle invasion in approximately 30% of cases. Besides, 20–25% of NMIBC bladder cancer progress to muscle invasion sometime during their natural history. Approximately 30% of patients diagnosed with muscle-invasive bladder cancer have undetected metastasis at the time of treatment of a primary tumor, while 25% of patients submitted to radical cystectomy present with lymph node involvement at the time of surgery [15].

Table 17 Classification of CIS according to clinical type [15, 46]

Classification	Definition
Primary CIS	Isolated CIS with no previous or concurrent papillary tumors and no previous CIS
Secondary CIS	CIS detected during follow-up of patients with a previous tumor that was not CIS
Concurrent CIS	CIS in the presence of any other urothelial tumor in the bladder

Table 18 Surveillance recommendations for bladder recurrence in non-muscle invasive bladder cancer [22]

Risk stratification	Follow up schedule
All patients	Initial cystoscopy within 3–4 months of completion of treatment
Low-risk:	Cystoscopy 6–9 months later, and then annually for at least 5 years
Intermediate-risk	Cystoscopy + cytology every 3–6 months for 2 years, then every 6–12 months for years 3–4, and then annually thereafter
High-risk:	Cystoscopy + cytology every 3–4 months for 2 years, then every 6 months for years 3–4, and then annually thereafter
Upper tract evaluation	Yearly for high-risk NMIBC, no specific recommendations for low- or intermediate-risk NMIBC Not routinely recommended for low-risk NMIBC

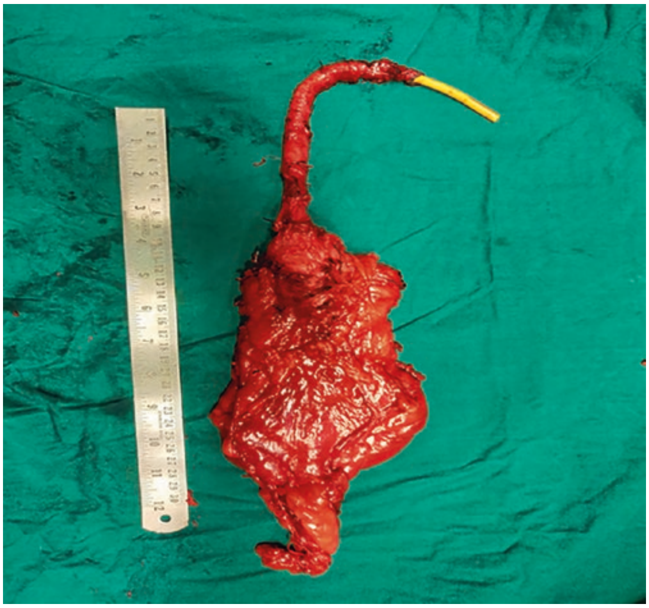
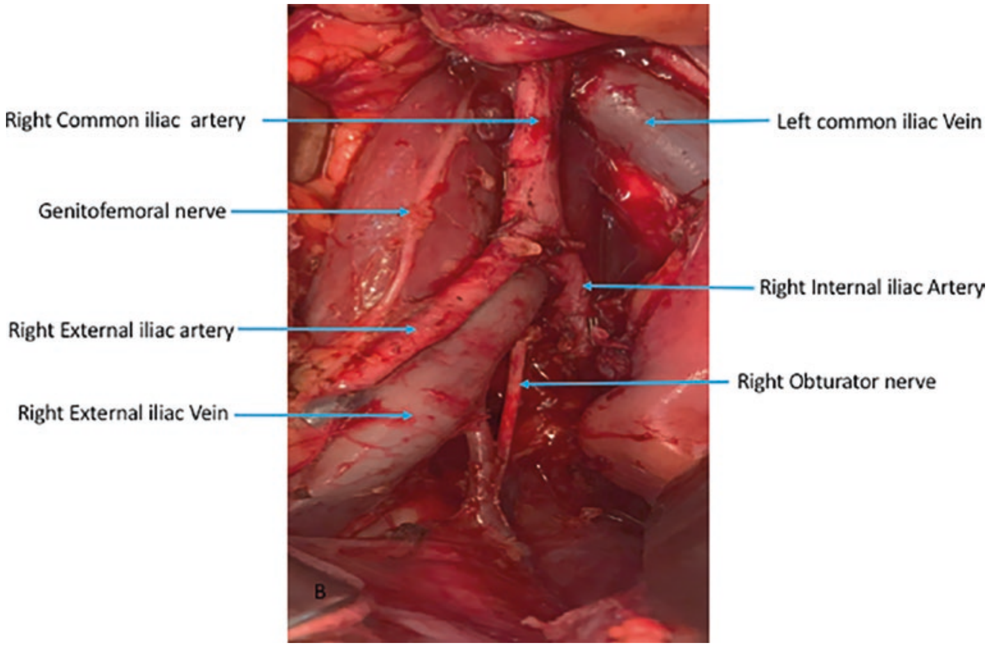


Fig. 4 En bloc specimen of radical cystoprostatectomy with urethrectomy

12.8.1 Surgery

Radical cystectomy is the preferred treatment for invasive bladder cancers in patients whose medical condition allows the major surgical procedure (Fig. 4). Pelvic lymphadenectomy is routinely performed as part of radical cystectomy for bladder cancers; however, there is a lack of consensus on the intent (therapeutic or staging/prognostic) and extent of lymph node dissection (Fig. 5). There is evidence from retrospective studies that extended lymphadenectomy improves outcome in patients with tumors confined to the bladder. However, no controlled

Fig. 5 Extended template of right pelvic node dissection


Right Common iliac artery
Left common iliac Vein
Genitofemoral nerve
Right Internal iliac Artery
Right External iliac artery
Right Obturator nerve
Right External iliac Vein
B

studies support extended lymphadenectomy as a curative treatment. Thus, limited or regional lymph node dissection is the recommended standard surgical method (Table 19) [47, 48]. Removal of more than 15 lymph nodes has been postulated to be both sufficient for the evaluation of the lymph node status as well as beneficial for overall survival in retrospective studies in the presence of gross nodal disease [15, 48].

Radical cystectomy is recommended for non-transitional cell carcinomas, which generally respond less to radiation and chemotherapy. However, despite adequate surgery, approximately 50% of patients will develop metastatic disease within 2 years, emphasizing the need for augmenting treatment in these patients. The 5-year survival rates after radical cystectomy alone in T2, T3a, T3b, and T4 disease are 63%, 57%, 31%, and 18%, respectively.

Partial cystectomy is very rarely indicated in muscle-invasive urothelial cancer. Patients, who are not fit for radical cystectomy with solitary muscle-invasive tumor at the dome, with no extravesical spread and negative random mucosal biopsies and intra-operative frozen section surgical margins can be considered for partial cystectomy.

12.9 Indications of Urethrectomy [49]

Urethrectomy may be done at the time of cystectomy or subsequently as a separate procedure in the following scenarios

1. A tumor involves the bladder neck in women or the prostatic urethra in men.
2. The positive urethral cut margin at the end of cystectomy.
3. Extensive involvement of the prostate stroma.

Table 19 Extent of lymph node dissection in bladder cancer [47]

Type of lymph node dissection	Definition
Limited	Lateral boundary: External iliac vein Medial boundary: Obturator nerve (Perivesical tissue and lymphatic tissue in obturator fossa)
Standard	Superiorly: bifurcation of the common iliac artery Inferiorly: circumflex iliac vein Medially: Internal iliac vessels Laterally: Genitofemoral nerve Floor: obturator fossa
Extended	Proximal boundary: crossing of ureter /common iliac artery. Rest landmarks as a standard template
Super extended	Proximal boundary: the origin of IMA. Rest landmarks as a standard template

12.10 Urinary Diversion or Reconstruction

The type of urinary diversion does not affect the oncological outcome. The advantage of orthotopic neobladder over other diversions in terms of quality of life remains a matter of debate. The terminal ileum and colon are the intestinal segments of choice for urinary diversion. The morbidity of orthotopic neobladder reconstruction is appreciable in terms of major complications and reoperation rates. Orthotopic neobladder reconstruction should be advised to suitable patients after cystectomy for organ-confined muscle-invasive bladder tumor. While discussing this option with the patient, the morbidity must be addressed [49].

Table 20 Classification of urinary diversion

Classification	Type of urinary diversion
1. Orthotopic	Orthotopic bladder substitution 1. Studder neobladder 2. Hautmann neobladder 3. Mainz neobladder
2. Heterotopic (a) Continent	1. Cutaneous (catheterizable stoma on the abdominal wall) Types: (a) Right colonic pouch (Indiana pouch, Florida pouch, Miami pouch, Penn pouch) (b) Ileal pouches (Koch ouch, Mainz pouch)
(b) Non-continent	1. Ileal conduit/colonic conduit/ jejunal conduit 2. Cutaneous ureterostomy
(c) Diversion to the gastrointestinal tract	1. Uretero-sigmoidostomy/rectal bladder

Table 21 Oncological principles of orthotopic neobladder reconstruction [50]

1	The patient must have a healthy urethra and adequate external sphincter function to maintain continence
2	The bowel segment should be de-tubularized and reconstructed into a spherical shape.
3	Ultimate storage volume should be at least 300 to 500 mL at low pressure

Table 22 Contra-indications to orthotopic neobladder

1. Prostatic urethral involvement
2. Positive urethral margins
3. Multiple bladder tumors or multicentric involvement of the urinary tract
4. Chronic kidney disease

The various options available are as follows:

- Incontinent conduit with an external stoma.
- Continent catheterizable reservoirs with an abdominal stoma.
- Bladder substitution (neobladder) procedures.

Table 20 classifies the types of urinary diversion. Table 21 [50] enumerates the principles governing orthotopic neobladder reconstruction. Table 22 and Table 23 enumerate the contraindications to neobladder reconstruction and management of morbidity related to neobladder.

Table 23 Management of neobladder morbidity (30–64%) [46]

Complications	Management
Immediate complications:	
Post-operative nausea and vomiting	1. Anti-emetic agent (decrease opioids) 2. Nasogastric intubation
Post-operative ileus	1. Chewing gum 2. Nasogastric intubation 3. Avoid fluid excess and hypovolemia
Ureteral catheter obstruction	1. Inject 5 cc saline in the ureteral catheter or 2. Increase volume infusion to increase diuresis
Urinary infection	1. No ureteral catheter removal and check the 3 drainages (ureters and neobladder) 2. Antibiotics
Uretero-ileal anastomotic leak	1. Check drainages 2. Watchful waiting
Anaemia	1. Iron supplements
Late complications:	
Incontinence	1. Urine analysis 2. USG (post-void residue) 3. Physiotherapy
Retention	1. Drainage 2. Self-catheterization education
Pyelonephritis	1. Antibiotics 2. Renal drainage (nephrostomy if necessary)
Pulmonary embolism	1. Heparinotherapy
Anastomosis stenosis (7%)	1. Renal drainage (ureteral catheter or nephrostomy)
Compressive lymphocele	1. Surgery (marsupialisation)
Ileal anastomosis leakage	1. Ileostomy, as soon as possible

12.11 Enhanced Recovery after Surgery Pathway Outcomes

ERAS study group was formed in 2001 with an emphasis on improving and standardizing perioperative care. In the setting of radical cystectomy, ERAS has shown benefits in reducing the incidence of postoperative especially gastrointestinal complications, and also shortens the length of hospital stay. So, continuous modifications of the ERAS pathway will help us in refining patient care and improve postoperative outcomes [51].

13 Minimally Invasive Surgery for Bladder Cancer

RARC as a minimally invasive technique is gaining wide acceptance, which seems non-inferior to open radical cystectomy. To date, randomized controlled trials comparing open with robotic- assisted radical cystectomy have shown lower estimated blood loss, lower blood transfusion, long operative time with similar oncologic outcomes, increased cost, decreased length of hospital stay, and similar perioperative complications. Hence, it is a technique that should complement and not substitute oncologic principles [52].

The RAZOR trial (Randomized Open Versus Robotic Cystectomy multi-institutional trial) has shown an increased presence of positive soft tissue margin in the initial learning curve, which is supposed to be a strong marker of poor prognosis but as the learning curve increases, the percentage of cases with positive margins decreases [53].

Robotic radical cystectomy with intracorporeal urinary diversion is the latest addition to the surgical armamentarium.

Additionally, robotic surgery has the distinct benefit of higher magnification and surgeon's comfort but the availability of robots and cost is a concern.

14 Role of Chemotherapy in Bladder Urothelial Carcinoma

14.1 Neoadjuvant Chemotherapy Before Radical Cystectomy

Although radical cystectomy is the standard treatment for patients with muscle-invasive bladder cancer, it leads to long-term cures in only 50% of patients. In order to improve these results, the use of neoadjuvant chemotherapy has been explored. The rationale for chemotherapy is based on the intention to treat micrometastatic disease, which is present at diagnosis prior to cystectomy or radical radiation therapy. Neoadjuvant chemotherapy administered before definitive local treatment (surgery or radiotherapy) has shown a survival benefit based on a meta-analysis of 3005 patients from 11 randomized trials. A meta-analysis showed that neoadjuvant chemotherapy decreased the risk of death by 14%, improved absolute disease-specific survival by 9%, and improved overall survival by 5% at 5 years ($p = 0.003$). This advantage in survival was seen for all muscle-invasive tumors and only patients who received a cisplatin-containing regimen benefited. Though the available data support the use of M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or CMV (cisplatin, methotrexate, vinblastine) as neoadjuvant chemotherapy, these regimens are less frequently used as phase 3 data in the metastatic setting suggested that a less toxic regimen of gemcitabine and cisplatin (GC) has similar efficacy to M-VAC. Neoadjuvant chemotherapy is not recommended in patients with poor performance scores and impaired renal function [20, 54].

14.2 Adjuvant Therapy

To date, there have been five published randomized trials of adjuvant chemotherapy and one meta-analysis, neither has provided sufficient data to support the routine use of adjuvant chemotherapy. The commonest regimens used are MVAC/CMV or CISCA. Although not convincingly shown to improve survival, it may be useful in patients with pT3–4 and/or N+ patients [20, 50].

14.3 Chemotherapy for Metastatic Bladder Cancer

Approximately 5–10% of bladder cancers are metastatic at presentation and another 40% of patients will develop metastatic disease during their clinical course, typically appearing in lymph nodes, lung, liver, or bone. Patients with good PS, adequate renal function, and only lymph nodal metastasis are considered as the best candidates for chemotherapy with approximately 15% having long-term survival. Methotrexate, vinblastine, doxorubicin (Adriamycin), cisplatin (M-VAC), and gemcitabine/cisplatin (GC) have prolonged survival up to 14.8 and 13.8 months, respectively. Since single-agent chemotherapy has shown low response rates, So, combination M-VAC chemotherapy is considered superior due to high response rates. Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of CR and survival. Either M-VAC or CMV has been considered the standard combination for metastatic bladder cancer. In an international randomized trial, M-VAC was compared with gemcitabine and cisplatin (GC). Both arms were found to be equivalent in terms of response rates, time to treatment failure, time to progressive disease, and overall survival. GC appeared to have a reduced toxicity profile as compared to M-VAC, making GC a new standard chemotherapeutic option in patients with metastatic bladder cancer. Second-line therapy should be considered within a clinical trial setting. If the patient has a good PS, single agents or paclitaxel/gemcitabine may be considered. Quality of life issues are very important considerations when deciding on further chemotherapy [20, 55, 56].

Table 24 Role of immunotherapy in metastatic urothelial carcinoma [20]

Study population	Immunotherapy drug	Target	Response rate (%)	Median progression-free survival (months)	Median overall survival (months)
Metastatic urothelial carcinoma	Gemcitabine plus cisplatin and ipilimumab	CTLA-4	23/36 (64%)	–	14.6
Muscle-invasive bladder cancer	Ipilimumab	CTLA-4	–	–	–
Post platinum therapy metastatic urothelial carcinoma	Atezolizumab	PD-L1	45/310 (15%) 26/100 (26%)	2.1	7.9
Post platinum therapy metastatic urothelial carcinoma	Pembrolizumab	PD-L1	8/29 (28%) 6/18 (33%)	2	12.7

14.4 Emerging Bladder Cancer Treatments

Bladder cancer has seen a substantial increase in drug development activity in the past 5 years. Recent developments in the field of immunotherapy have shown some rays of hope in the post-platinum era in terms of good response rates, especially in platinum-resistant cases or those patients who are ineligible for cisplatin owing to renal impairment or other medical comorbidities (Table 24) [20].

15 Role of Radiotherapy

For stage Ta, T1, or Tis disease, adjuvant radiation is not indicated [57]. However, in recurrent Ta-T1 disease after BCG therapy but without extensive Tis who are not candidates for cystectomy, concurrent chemoradiotherapy is a valid alternative with comparable outcomes [58, 59].

15.1 Bladder Preservation

For T2-T3 muscle-invasive bladder cancer, the standard treatment had been radical cystectomy. But now, there is evidence [59–61] to show similar survival outcomes with up to 80% bladder preservation rate and limited grade III/IV toxicities using trimodality treatment which comprises radiotherapy, chemotherapy, and surgery. This involves neoadjuvant chemotherapy followed by maximal Transurethral resection of bladder tumor (TURBT) followed by radical radiotherapy with concurrent chemotherapy, reserving cystectomy as a salvage option. Older series [59] have shown a good response to radiotherapy alone in patients unfit for surgery. However, outcomes of bladder preserving CTRT are expectedly better in patients with good bladder function pre-radiotherapy, without extensive CIS or tumor-related hydronephrosis.

In the best hands, overall survival rates with bladder preservation are comparable to radical cystectomy [62, 63]. Pooled analysis of 6 RTOG trials with clinical T2 to T4a tumors has shown a complete response rate of 69% following chemo-radiotherapy. The 5-year disease-specific survival (DSS) rate was 71% and 5-year OS was 57%. Of the 205 patients alive at 5 years, 80% had intact bladder [64]. Routine follow-up with cystoscopy and exfoliative urine cytology is warranted in view of the high local recurrence rate (36%). Better outcomes have been reported with the addition of concurrent chemotherapy to RT [61].

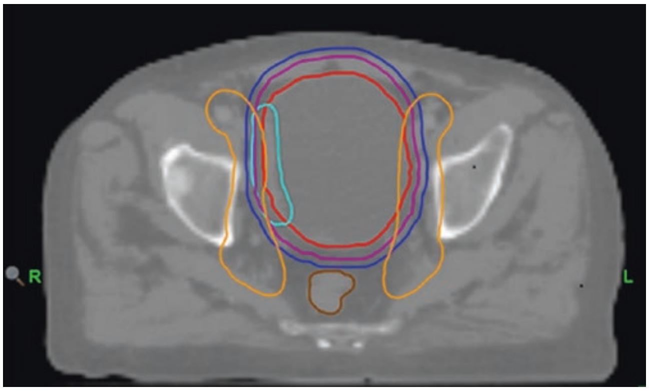


Fig. 6 Axial view of planning CT scan showing the three PTV margins to the bladder

Conformal three-dimensional RT techniques have replaced two-dimensional approaches for radiotherapy delivery (Fig. 6). Intensity-modulated radiation therapy (IMRT) with image-guided radiotherapy (IGRT) has allowed for dose escalation as well as minimizing genitourinary and gastrointestinal toxicities. The dose consists of 60 to 64 Gy to the entire bladder, prostatic or proximal urethra, and 50 Gy to the regional lymph nodes This is followed by restaging cystoscopy. "Plan of the day" is an adaptive radiotherapy technique that involves generating multiple planning target volumes (PTV) using anisotropic margins and treating the patient with the appropriate PTV for that particular day. This ensures the best possible coverage of the bladder resulting in better dose delivery and reduced toxicity to the small bowel [65, 66].

15.2 Role of Adjuvant Radiotherapy

Adjuvant postoperative radiotherapy for pT3 and pT4 bladder cancer patients has been studied in small prospective trials (particularly for squamous cell carcinomas) [67]. Two-year outcomes and overall adjusted hazard ratios (HRs) for chemotherapy plus RT versus chemotherapy alone have been reported 68% vs. 56% (HR, 0.53; 95% CI, 0.27–1.06; $P = 0.07$) for disease-free survival, and 71% vs. 60% (HR, 0.61; 95% CI, 0.33–1.11; $P = 0.11$) for overall survival [68]. The role of adjuvant RT is being currently investigated in large phase III randomized trials [69, 70] including BART (Bladder Cancer Adjuvant Radiotherapy) trial [71] from Tata Memorial Hospital, Mumbai for patients with pT3 and pT4 disease, lymph node positivity, close/positive margin of resection as well as a number of nodes dissected at surgery <10.

Table 25 Recurrence-free and overall survival after radical cystectomy [48]

		Recurrence-free		Overall survival	
Pathologic stage		5 years (%)	10 years (%)	5 years (%)	10 years (%)
pTo, pTa, pTis		88	85	84	67
	N-	89	85	85	67
	N+	60	60	40	40
pT1	(all pts)	80	75	74	51
	N-	83	78	76	52
	N+	43	43	50	42
pT2	(all pts)	81	80	72	56
	N-	89	87	77	57
	N+	50	50	52	52
pT3a	(all pts)	68	65	58	39
	N-	78	76	64	44
	N+	41	37	40	26
pT3b	(all pts)	47	46	38	22
	N-	62	61	49	29
	N+	29	29	24	12
pT4a	(all pts)	44	41	33	22
	N-	50	45	44	23
	N+	33	33	26	20
Organ-confined	(all pts)	80	77	74	54
	N-	85	82	78	56
	N+	46	44	45	37
Extravesical	(all pts)	46	44	37	22
	N-	58	55	47	27
	N+	30	30	25	17
All patients		46	44	37	22
LN- pts		78	75	69	49
LN+ pts		35	34	31	23
Total group		68	66	60	43

N-, without lymph node involvement (node-negative); N+, with lymph node; pts, patient pathologic stage is based on the 1987 TNM system

Organ confined, including pTo, pTa, pTis, pT1, pT2, and pT3a bladder tumors

Extravesical, including pT3b and pT4 bladder tumors

Table 25 shows the recurrence-free and overall survival after definitive local therapy for MIBC.

Palliative RT is used for bone metastasis, pain relief, as well as for achieving hemostasis in advanced, hemorrhagic tumors refractory to anticoagulants. Table 26 enumerates the management options for recurrent disease.

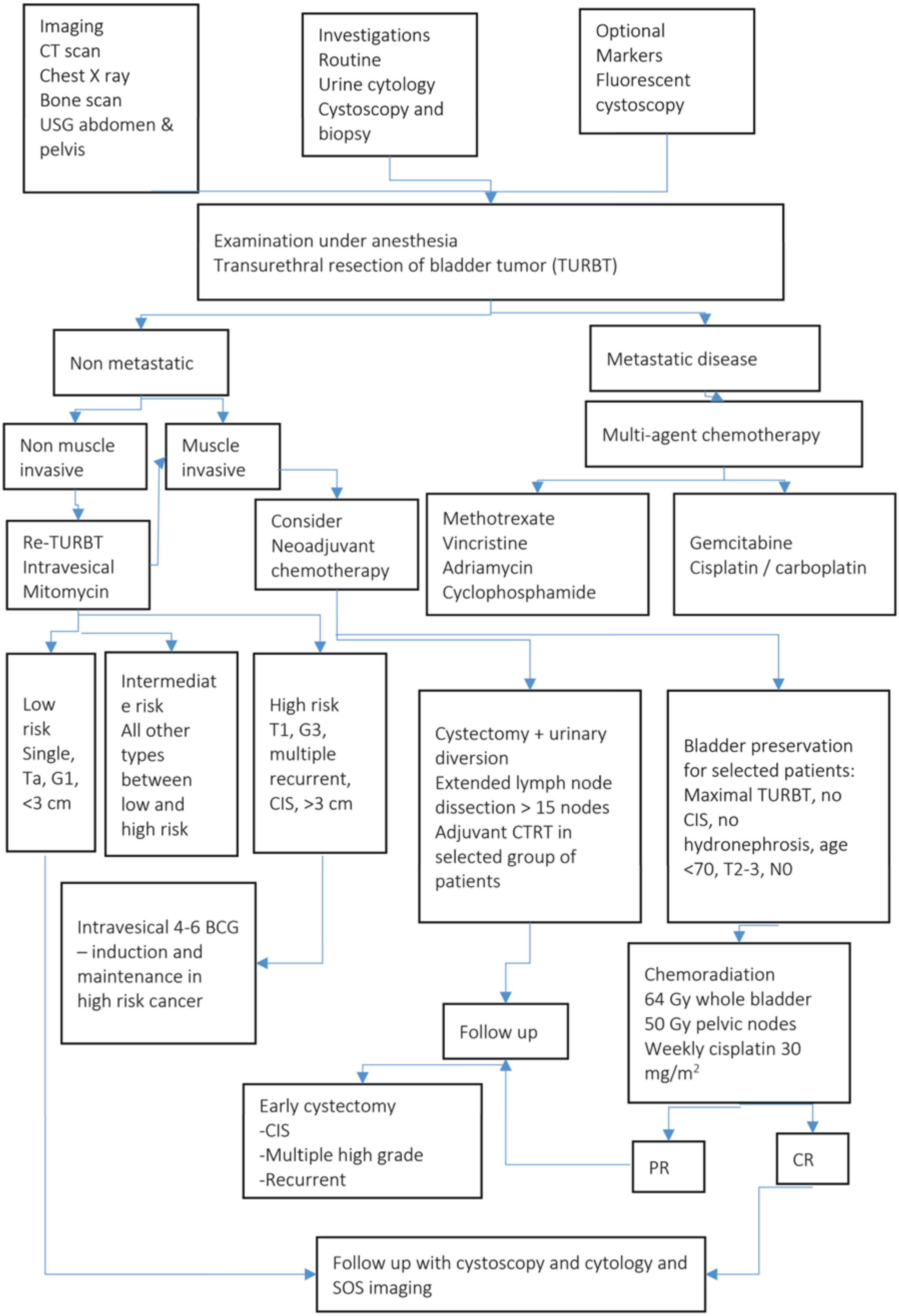
How We Do It at TMC

- Patients are referred to TMC for bladder cancer based on sonography findings of mass in the bladder, or after cystoscopic biopsy of bladder mass or after TURBT of bladder tumor or occasionally with clot retention and gross hematuria.
- Based on available imaging, biopsy, and TURBT histopathology these tumors are suspected to be NMIBC, MIBC, or equivocal.
- All histopathologies reported elsewhere are reviewed by GU pathologists at TMC to confirm concordance of grade, and depth and rule out variant histology.
- Cystoscopic evaluation and mapping of all tumours is done. In patients with definite MIBC or metastatic disease cystoscopy can be skipped. Some patients require emergency clot evacuation and TURBT because of gross hematuria at presentation.
- Patients with obstructive uropathy at presentation undergo unilateral or bilateral nephrostomy which stays till definitive management is done. Retrograde DJ stenting is rarely feasible in these patients.

Table 26 Management of recurrent disease including specific palliative measures [46]

Site of recurrence	Management strategies
Local recurrence	Offer radiotherapy, chemotherapy, and possibly surgery as options for treatment, either alone or in combination.
Distant recurrence	Offer chemotherapy as the first option, and consider metastasectomy in case of a unique metastasis site.
An unresectable tumor (T4b) with bleeding, pain, dysuria, and urinary obstruction	Silver nitrate, alum, formalin instillation, pall RT, angioembolization for bleeding Unilateral/bilateral nephrostomy or DJ stenting for obstructive uropathy Palliative cystectomy with urinary diversion or only urinary diversion as a last resort

- Patients with NMIBC are categorized into low, intermediate or high risk based risk stratification suggested in EAU guidelines.
- All high grade and T1 patients who have undergone TURBT earlier undergo restaging TURBT irrespective of presence or absence of detrusor in initial histopathology.
- Perioperative single instillation of Mitomycin C is done in all patients undergoing TURBT. This is done preferably within 6 h and definitely within 2 h of surgery unless there is a perforation or gross hematuria post-surgery.
- In all intermediate and high-risk patient's induction and maintenance intravesical BCG is instilled as per Lamm's regime. Patients are assessed for BCG toxicity before each instillation.
- Patients with MIBC or very high risk NMIBC or those with variant histopathology are considered for radical cystectomy or bladder preservation.
- GFR estimation of all MIBC patients is done by plasma sampling. Differential GFR is estimated by renogram when required.
- Based on patients GFR and performance status they are evaluated for eligibility of cisplatin-based neoadjuvant chemotherapy. If eligible they undergo three cycles of gemcitabine and cisplatin before undergoing cystectomy.
- Radical cystectomy includes extended pelvic lymph node dissection. Based on disease profile and patient's preference either an ileal conduit or neobladder diversion is constructed. Ileal conduit is the most common diversion done at TMC. All patients get nutrition clinic reference at the time of decision for cystectomy and post-operative stoma clinic reference is also done.
- Patients who could not receive neoadjuvant chemotherapy are considered for adjuvant chemotherapy based on histopathology. Eligible patients are enrolled in Bladder Adjuvant Radiotherapy (BART) trial. They could receive adjuvant radiotherapy if randomized to treatment arm.
- Figure 7 depicts the management algorithm for bladder cancer patients at TMH.
- Surveillance of all NMIBC and MIBC patients is done as per EAU guidelines.
- Patients with metastatic disease are considered for palliative chemotherapy, pain management, nephrostomy, angioembolization, palliative radiotherapy based on their presentation and performance status.


Imaging
CT scan
Chest X ray
Bone scan
USG abdomen & pelvis
Investigations
Routine
Urine cytology
Cystoscopy and biopsy
Optional
Markers
Fluorescent cystoscopy
Examination under anesthesia
Transurethral resection of bladder tumor (TURBT)
Non metastatic
Metastatic disease
Non muscle invasive
Muscle invasive
Multi-agent chemotherapy
Re-TURBT
Intravesical
Mitomycin
Consider
Neoadjuvant
chemotherapy
Methotrexate
Vincristine
Adriamycin
Cyclophosphamide
Gemcitabine
Cisplatin / carboplatin
Low risk
Single, Ta, G1, <3 cm
Intermediate risk
All other types between low and high risk
High risk
T1, G3, multiple recurrent, CIS, >3 cm
Cystectomy + urinary diversion
Extended lymph node dissection > 15 nodes
Adjuvant CTRT in selected group of patients
Bladder preservation for selected patients: Maximal TURBT, no CIS, no hydronephrosis, age <70, T2-3, N0
Intravesical 4-6 BCG – induction and maintenance in high risk cancer
Follow up
Chemoradiation
64 Gy whole bladder
50 Gy pelvic nodes
Weekly cisplatin 30 mg/m²
Early cystectomy
-CIS
-Multiple high grade
-Recurrent
PR
CR
Follow up with cystoscopy and cytology and SOS imaging

Source - NCG guidelines for common cancers

Fig. 7 Stage-wise prognosis algorithm

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Upper Tract Urothelial Cancer

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Abbreviations

BCG	Bacillus Calmette-Guérin
CT	Computerized tomography
FISH	Fluorescence *in situ* hybridization
HNPCC	Hereditary nonpolyposis colorectal carcinoma
HR	Hazard ratio
LNU	Laparoscopic nephroureterectomy
MMC	Mitomycin-C
MRI	Magnetic resonance imaging
PUNLMP	Papillary urothelial neoplasia of low malignant potential
RNU	Radical nephroureterectomy
RT	Radiation therapy
URS	ureteroscopy
UTUC	Upper tract urothelial carcinoma

1 Introduction

Upper tract urothelial cancers (UTUC) include the neoplasms arising from the lining of the urinary tract anywhere between the pelvicalyceal systems to the distal ureter. UTUC share a few similar features with urothelial carcinoma bladder; however, they tend to be rare and more advanced at the time of presentation. Radical nephroureterectomy (RNU) with ipsilateral bladder cuff excision is the gold-standard treatment. However, in recent years, nephron-sparing approaches have been widely gaining popularity, especially in low-risk diseases [1].

2 Incidence and Epidemiology

Nearly all cases of urothelial carcinoma are urinary bladder cancers, whereas UTUC accounts for just 5–10% of all urothelial malignancies. However, ~60% of UTUCs are usually found to be invasive at the time of diagnosis, compared with only 15–25% of bladder tumors. The peak incidence of UTUC is at 75–79 years [2, 3].

The most common location for this tumor is the renal pelvis. When it comes to the ureter, the distal ureter is the most affected part. Based on the location, the incidence of ureteric tumors is as follows: lower ureter in 70%, mid ureter in 25% and then upper ureter in 5% of the cases [4, 5].

Concurrent urothelial carcinoma bladder is seen in 17% of UTUC cases. Recurrence of urothelial tumors in the bladder occurs in 22–47% of the cases and recurrence in the contralateral upper urinary tract is seen in 2–6% [6, 7].

Many environmental and genetic factors are implicated in the development of UTUC.

2.1 Environmental Factors

Tobacco consumption is the most important contributing factor in the development of UTUC. Among smokers, the relative risk for developing upper tract neoplasms is 2.5 to 7-fold higher than that for nonsmokers [8].

Balkan endemic nephropathy, a kind of degenerative interstitial disease, is observed in people living in Balkan countries (i.e., Bulgaria, Greece, Romania and the former Yugoslavia). Dietary exposure to aristolochic acid, which is derived from Aristolochia plants, was found to be the culprit carcinogen. A similar association with the consumption of

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Chinese herbal products which contain *Aristolochia fangchi* and Chinese herb nephropathy was postulated. Both the diseases are associated with the development of UTUC. Surprisingly, the incidence of bladder urothelial carcinoma is not affected. Mutation of the p53 gene was found to be a consequence of aristolochic acid exposure [9, 10].

An unusually high incidence of UTUC was also reported from "Blackfoot disease" endemic areas, especially in southern Taiwan. It's a type of vasculitis that occurs due to arsenic-contaminated water [11]. Phenacetin use with papillary necrosis has also been recognized as a risk factor for UTUC [12].

2.2 Genetic Factors

Hereditary nonpolyposis colorectal carcinoma (HNPCC) otherwise called Lynch syndrome is associated with the development of colorectal and endometrial tumors due to various DNA mismatch repair abnormalities. The relative risk of developing UTUC in these cases is 22 folds approximately [13].

3 Clinical Presentation

The common presenting features of UTUC are microscopic or macroscopic hematuria (56–98%), loin pain (20–40%) and lumbar mass (10–20%). About 15% of patients are incidentally detected [14].

4 Evaluation and Work-up

4.1 Imaging

4.1.1 Ultrasonography (USG)

The detection rate of renal pelvis carcinoma using the USG is moderate (82%). But detection of ureteric tumors can be as low as 12%. However, the USG can demonstrate secondary signs caused by ureteric tumors such as dilatation of the ureter and pelvicalyceal system [14].

4.1.2 Computerized Tomography (CT)

Multiphasic CT urography yields the maximum diagnostic accuracy for upper tract neoplasms with a sensitivity and specificity ranging from 0.67 to 1.0 and 0.93 to 0.99, respectively. It can also detect urolithiasis and renal tumors; hence, it has become the gold-standard investigation for hematuria evaluation (Fig. 1). However, flat upper tract lesions can be missed on CT. Ureteric wall thickening and periureteric fat stranding if present are red flags in such cases [15, 16].

4.1.3 Magnetic Resonance Imaging (MRI)

MRI is useful in individuals who cannot undergo CECT due to contraindications related to radiation exposure or iodinated contrast administration. Documented sensitivity of contrast MRI for tumors <2 cm is 0.75. MRI is unreliable in detecting urolithiasis, which is a major limiting factor for being a primary imaging modality for hematuria. Similar to CT scans, MRI can also miss flat lesions because of motion artifacts [14, 16].

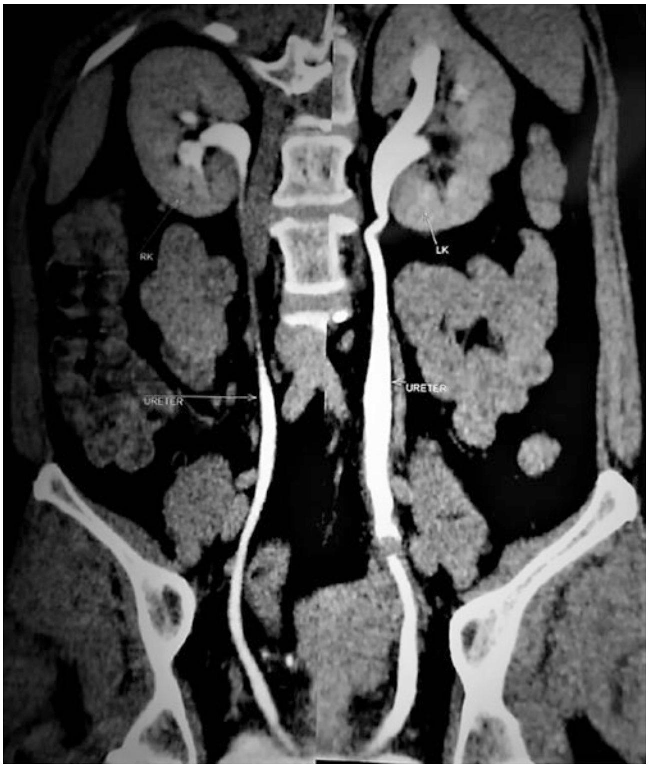


Fig. 1 CT scan showing left ureteric tumor (Arrow head)

4.2 Endoscopy

Clinicians should have a high index of suspicion for UTUC when cystoscopy is normal with positive urine cytology. In such a scenario, selective ureteric catheterization followed by barbotage or brushing is performed. The sensitivity of ureteral washing and brushing in detecting UTUC is 80% and 90%, respectively. Additionally, retrograde urethrography can help to identify any filling defects, often known as the "goblet sign" (Fig. 2). Selective urine samples for cytology should be collected before retrograde urethrography because administration of hyperosmolar contrast material can cause alteration of the microscopic cytology features of the tumor cells [5, 17].

Recent improvements in endoscopic technology including fiber optics and flexible ureteroscopes with active deflection are allowing better visualization of the urinary tract and if needed, a biopsy of the suspected lesions (Fig. 3). The specificity of ureteroscopic biopsy to determine the tumor grade is between 75% and 92%. However, accurate assessment of tumor invasion is very difficult [14, 18].

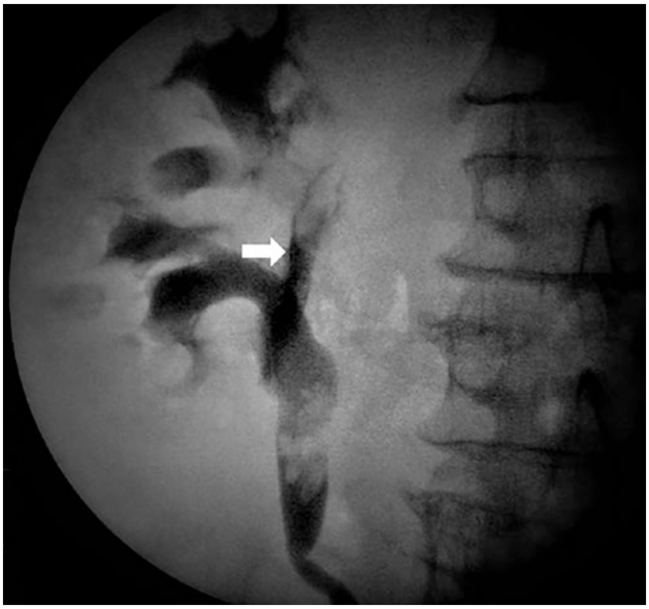


Fig. 2 RGU showing filling defect in right upper ureter (Arrow head)

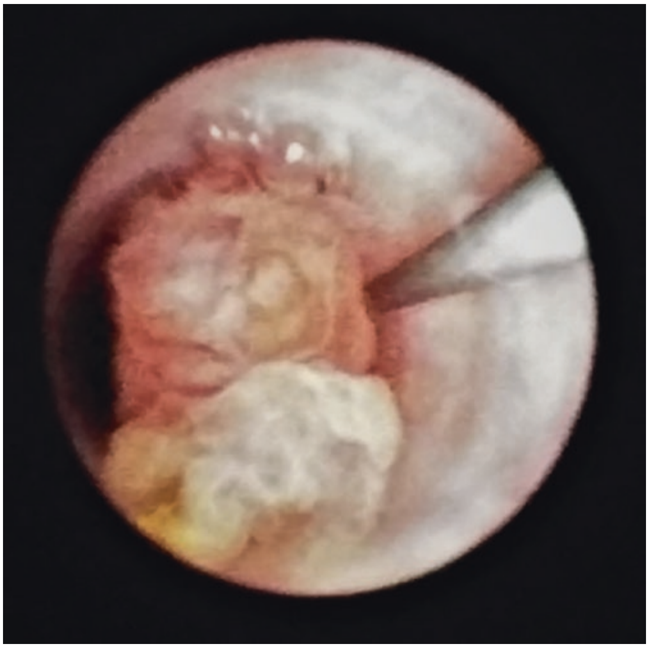


Fig. 3 Ureteroscopic view of ureteric tumour

4.3 Tumor Markers

Urinary cytology for UTUC is generally less sensitive than it is for urothelial carcinoma bladder. However, ureteric washings improve the diagnostic yield. Fluorescence *in situ* hybridization (FISH) appears to be more sensitive than urinary cytology and has equal specificity in detecting UTUC [19]. The nuclear matrix protein (NMP22) test has better sensitivity but lower specificity than urinary cytology [20].

4.4 Pathology

The UTUCs can manifest as noninvasive papillary tumors, carcinoma *in situ* (CIS; High-grade flat lesion) and invasive tumors. These lesions share similar features with bladder urothelial carcinoma on histology. However, early muscle invasion or periureteric spread can happen because of the relative thinness of the muscle layer of the upper urinary tract when compared with the bladder. WHO-2004 grading distinguished three kinds of noninvasive neoplasms, i.e., papillary urothelial neoplasia of low malignant potential (PUNLMP), low-grade carcinomas and high-grade carcinomas. Benign urothelial papillomas are excluded from this classification [21].

Variants of urothelial carcinoma include squamous cell, glandular, sarcomatoid, micropapillary, neuroendocrine and lymphoepithelial tumors. Their incidence is as high as 25% of upper tract neoplasms. Variants are considered to be relatively aggressive tumors [22].

The TNM classification 2017 is the presently used standard staging system and can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 754, Chapter no. 61, Renal Pelvis and Ureter, Table: Definition of TNM which can be accessed at https://www.pathologyoutlines.com/topic/bladderstagingrenalpelvis.html

When it comes to Renal pelvic tumors, invasion into the renal pelvis is classified as T3 disease. Subclassification of this category may differentiate between microscopic (pT3a) versus macroscopic (pT3b) renal parenchyma infiltration or invasion of peripelvic adipose tissue [23].

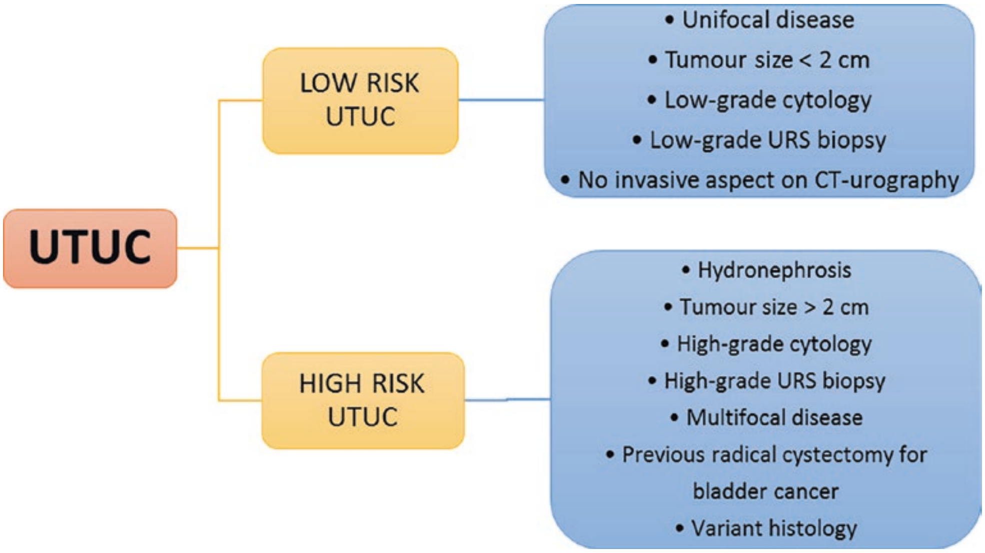
4.5 Genetic Counseling

HNPCC (Lynch syndrome) must be suspected in individuals of UTUC at a younger age at presentation or personal/family history of HNPCC spectrum of disorders. These patients subsequently should undergo germline DNA sequencing to confirm the diagnosis. Once HNPCC syndrome is diagnosed, the key to management is good surveillance to prevent disease recurrence as well as the screening of first-degree relatives for the HNPCC spectrum of diseases [24].

5 Principles of Management (an Integrated Brief Overview of Rx Philosophy)

The management of upper tract urothelial tumors has changed significantly lately. Numerous prognostic factors have helped to guide therapy and predict survival outcomes. Technologic advancements in imaging and telescopic

Fig. 4 Risk stratification of UTUC



visualization of urinary tract have helped in early and precise diagnosis and bettered follow up.

Treatment primarily based on the risk stratification of the tumor (Fig. 4). Treatment of low-risk noninvasive UTUC consists of conservative nephron-sparing surgery (e.g., endoscopic treatments, segmental resection) and adjuvant topical therapies (e.g., mitomycin-C). Depending on tumor size, number, location and access that allows complete tumor ablation, retrograde approach via ureteroscopy and ureterorenoscopy is preferred. Percutaneous antegrade approach is chosen when the location and tumor characteristics do not allow complete ablation through a retrograde approach. Radical nephroureterectomy is primary treatment option for high risk non metastatic tumor. Minimal invasive approach is preferred at least for renal part of radical nephroureterectomy as most upper tract urothelial tumors are not large or bulky. A diverse approach with various combinations of laparoscopic, open and endoscopic techniques is used for distal ureterectomy with bladder cuff excision. A cisplatin-based perioperative chemotherapy appears to have benefit in overall survival and disease-free survival has been proven by number of comprehensive studies [25]. Radiotherapy has no role as adjuvant treatment alone or as an adjunct to chemotherapy [26].

Table 1 Indication for radical nephroureterectomy [27]

Guidelines for RNU if any of the following are present:
• Suspicious imaging findings suggesting invasive UTUC
• High-grade tumor as demonstrated by urinary cytology and/or biopsy
• Multifocality with both functional kidneys
• Bulky tumors (i.e., > 2 cm)
• Variant histology

Table 2 Techniques for resection of the distal ureter and bladder cuff excision

Techniques for resection of the distal ureter and bladder cuff excision
1. Open technique
2. Transurethral resection of the ureteral orifice "pluck" technique
3. Intussusception (stripping) technique
4. Transvesical ligation and detachment technique
5. Total laparoscopic technique

6 Surgical Management

6.1 Radical Nephroureterectomy

The radical nephroureterectomy with excision of the bladder cuff is the standard treatment for UTUC (Table 1) as it fulfills all criteria for successful oncological surgery: removal of the entire tumor with an adequate margin, control of local recurrence, and control of the anatomical spread of the tumor. The intramural portion of the ureter including its orifice and a small circumferential cuff of the bladder has been mandatory because it is the part of the urinary tract at considerable risk of tumor recurrence [28]. Various techniques have been described to deal with distal ureter and bladder cuff excision (Table 2). All these techniques are equivalent for excision of the bladder cuff exception of ureteral stripping [29].

6.2 Adrenalectomy

If there is adrenal seeding or contiguous spread from a pelvic tumor, ipsilateral adrenalectomy is performed. There was no significant difference in 5-year survival, metastasis-free survival, or cancer-free survival regards to the role of adrenalectomy with localized UTUC treated by nephroureterectomy between the two groups [30].

6.3 Minimal Invasive RNU

When adhered to strict oncological principles, Laparoscopic RNU is safe in experienced hands. Multiple studies report having less blood loss, reduced postoperative pain and decreased length of stay in the laparoscopic group. However, oncological outcomes from this study show no statistically significant difference between laparoscopic and open surgery in terms of 5-year cancer-specific survival (89.9% vs. 78.8%) and 5-year metastases free survival (74.4% and 72.5%) [27, 31, 32]. Strong data is still lacking for the robotic approach, and studies are ongoing to establish its safety and benefit over the open approach [33].

6.4 Lymphadenectomy (LND)

The anatomic sites have not been clearly outlined for lymphatic drainage of the upper tract. The utilization of an LND template is probably going to own a larger impact on patient survival than the number of removed lymph nodes [34]. Lymph node positivity is reported in just 2.2% of T1 vs. 16% of pT2–4 tumors, and hence, lymphadenectomy benefited only high-grade, high-stage diseases [35]. A higher T stage increases in the likelihood of lymph node-positive disease [36]. An anatomical template-based approach should always be considered for dissection as it improves oncological outcomes [37].

6.5 Adjuvant Bladder Instillation

There is a 22–47% bladder recurrence rate after RNU for UTUC. One postoperative dose of intravesical therapy (mitomycin-C) shortly after surgery (< 72 h) proven by a meta-analysis and prospective randomized trials [38] have shown that reduces the chance of bladder tumor recurrence [39].

6.6 Conservative Surgery

The conservative treatment for UTUC includes various segmental resections or ablation via open, minimal invasive (laparoscopic, robotic or endoscopic) techniques (Table 3).

The conservative management of UTUC is as follows:

- Ureteroscopic management.
- Percutaneous approach.
- Ureteroureterostomy with adequate margins indicated for:
  - Ta low-grade tumors of the upper two-thirds of the ureter if not feasible for removal by endoscopic means.
  - In high-grade or high T stage tumors when renal preservation is a goal.
- Tumors in the distal ureter preclude its removal by endoscopic, distal ureterectomy and ureteric reimplant is performed [27].

Table 3 Recommendations for conservative management of UTUC

Recommendations for conservative management of UTUC
• Unifocal tumor
• Tumor size less than 2 cm
• Cytology or biopsy proven low grade
• Noninfiltrative lesion on CTU
• Patient understanding of close follow-up
• Inadequate renal reserve (chronic renal impairment or solitary kidney)
• Risk of bilateral disease (e.g., genetic, Balkan nephropathy)
• Significant comorbidity
• Palliation

6.7 Ureteroscopic Management (Table 4)

Ureteroscopy (URS) serves not only as a diagnostic modality but also for therapeutic purposes. For tumors in the upper ureter or in the renal pelvis which are difficult to access, a flexible ureteroscope which has a deflection angle of up to 270 ° can be used. Holmium or neodymium: yttrium–aluminum–garnet lasers are most frequently used for tumor ablation.

The grade of the disease is an important factor for successful ureteroscopic outcomes. In a study, the 5-year disease-specific survival (DSS) was 100% for Grade 1 tumors, 62.5% for Grade 2 disease and 55.6% for Grade 3 [41]. The DSS is similar for endoscopic and laparoscopic nephroureterectomy for low-Grade disease.

6.8 Percutaneous Management (Table 5)

Tumors difficult to access or when complete ablation is not achievable via retrograde approach like bulky tumor in the pelvis or upper ureter, direct access to the collecting system via percutaneous access is preferred. This is also the preferred approach in patients with suspected upper tract recurrence with a background of cystectomy with diversion for bladder carcinoma [42].

The outcomes antegrade are similar to retrograde treatment although invasive. With technological development and advances in flexible ureteroscopes with increased deflection, percutaneous methods are being used less.

Table 4 Ureteroscopic management [40]

Advantages of the ureteroscopic approach include:
• Preservation of renal function
• Reduced morbidity
• Shorter hospital stay
• Avoiding overtreatment for low-grade noninvasive disease
Disadvantages of the ureteroscopic approach include:
• Inability to treat larger tumors in one session
• Difficulty accessing upper ureteric or lower calyx tumors
• Understaging tumors
Risks of ureteroscopic treatment include:
• Ureteric perforation or avulsion causing extraluminal tumor spillage
• Ureteric strictures
• Residual disease
• Subsequent tumor upstaging and progression requiring RNU

Table 5 Percutaneous management [42]

Advantages of the percutaneous approach include:
• Better visualization
• Access to any location in the collecting system
• Treatment of large tumors in one session
• Deeper biopsies for accurate staging
• Adjuvant treatment can be administered through the nephrostomy tube left in the collecting system at the end of the procedure
• The same tract can be used for repeated procedures
Complications and risks of the percutaneous approach include:
• Bleeding requiring blood transfusions
• Obstruction of the pelviureteric junction from stricture
• Surrounding organ and pleural injury
• Risk of tumor cell seeding along the tract due to the disruption of the collecting system to gain entry

6.9 Adjuvant Therapy Following Endoscopic Treatment

To prevent disease recurrence and progression in patients with superficial bladder urothelial carcinoma, intravesical Mitomycin-C (MMC) and Bacillus Calmette-Guerin (BCG) is administered. There is limited evidence supporting the use of these adjuncts and the lack of randomized controlled trials, even though we may believe to have similar outcomes in the context of UTUC [42, 43].

These agents (MMC and BCG) can be delivered percutaneously through a nephrostomy tube, via a ureteric catheter following ureteroscopic tumor ablation retrogradely, or can be instilled in the bladder as it might reflux up via indwelling ureteric stent. There are no clear guidelines at present regarding the frequency, dosage and time of instillation of these agents in the management of UTUCs.

7 Medical Management

7.1 Neoadjuvant Chemotherapy (Table 6)

There are 60–75% pathological downstaging rates in some phase 2 trials assessing the role of neoadjuvant chemotherapeutic regimens in high-grade UTUC [46]. The patients receiving neoadjuvant chemotherapy had significantly longer 5-year overall survival (44% vs. 29%) compared who had surgery alone, with an adjusted hazard ratio (HR) of 0.47 (95% CI 0.22 to 0.99, $p = 0.047$) in a recent retrospective study [44].

7.2 Adjuvant Chemotherapy (Table 7)

There is evidence supporting adjuvant chemotherapy showing an advantage in overall survival with an HR of 0.43 (95% CI 0.21 to 0.89, $p = 0.023$) and disease-free survival with an HR of 0.49 (95% CI 0.24 to 0.99, $p = 0.048$) which comes from a meta-analysis of nine retrospective cohort studies [25]. The regimen of choice should be cisplatin based for adjuvant chemotherapy for patients with UTUC. A multi-institutional study showed favorable recurrence-free survival rates in patients who received adjuvant methotrexate, vinblastine, doxorubicin and cisplatin compared with those who received gemcitabine and cisplatin (71.4% vs. 48.2%, $p = 0.022$) [47].

A randomized POUT trial in UTUC has shown a benefit of using adjuvant chemotherapy in pT2–pT4 or LN-positive patients. Adjuvant chemotherapy has improved disease free survival and is better tolerated. As efficacy was favoring the chemotherapy arm, the recruitments in the trial were terminated early [48].

Table 6 Neoadjuvant chemotherapy [44]

Rationale of neoadjuvant chemotherapy
1. Able to tolerate chemotherapy with two functioning kidneys prior to RNU
2. Pathological downstaging gives clinicians important prognostication information
3. Level I evidence from urothelial carcinoma of the bladder recommending neoadjuvant chemotherapy prior to radical cystectomy [45]
Disadvantages of neoadjuvant chemotherapy
1. A delay to definitive surgical management, particularly in chemo resistant disease
2. Increase in perioperative morbidity
3. Overtreatment in patients who may simply have low-risk disease

Table 7 Adjuvant chemotherapy [25]

Advantages of adjuvant chemotherapy include:
• The availability of accurate postoperative pathological staging in order not to overtreat noninvasive disease
• Eradication of any subclinical micro metastases in order to maximize a patient's survival
Disadvantages of adjuvant chemotherapy include:
• Subjecting patients to potentially nephrotoxic chemotherapy after removal of one kidney

8 Radiation Management

The rationale for adjuvant radiation therapy (RT) is to decrease the risk of local recurrence after radical surgery for locally advanced disease (stage T3 to T4, N+). Because of a paucity of data, the role of radiation in the adjuvant management of UTUC is poorly clarified. A 3-year local recurrence-free survival rates were 89% vs. 61% in the RT vs. non radiation groups ($P = 0.01$) in patients with stage III/IV UTUC [49]. Fan et al. demonstrated improved overall survival for patients receiving adjuvant chemoradiation following surgery vs. chemotherapy and salvage radiation therapy [50]. However, another study reported no additional survival benefit compared to standard surgical therapy, as 5-year overall survival rates and recurrence-free survival rates were 49% and 30%, respectively, proving that RNU alone provides a high local control [51]. Also, for high-stage disease, adjuvant radiation without chemotherapy does not preclude chances of metastasis. The present data supporting is retrospective and small; however, there is a role for combined chemo-radiation in patients with advanced disease with adverse features.

9 Stage-Wise Management Algorithms (Figs. 5 and 6)

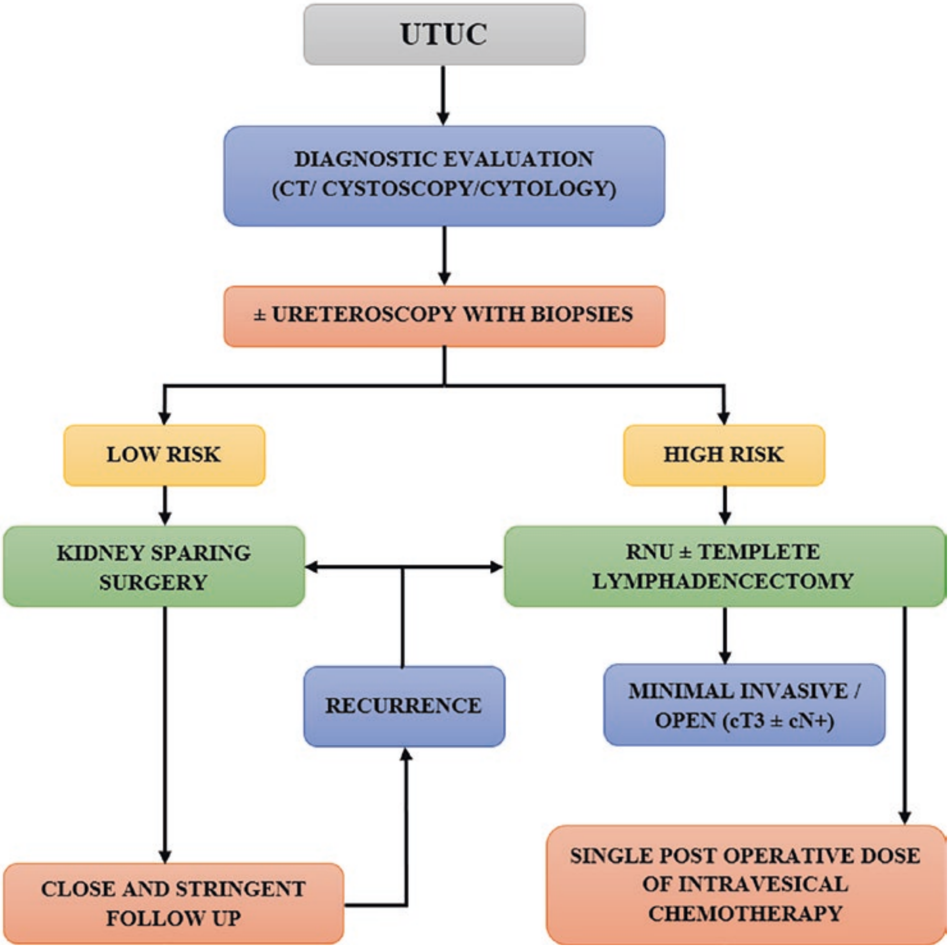

UTUC
DIAGNOSTIC EVALUATION (CT/ CYSTOSCOPY/CYTOLOGY)
± URETEROSCOPY WITH BIOPSIES
LOW RISK
HIGH RISK
KIDNEY SPARING SURGERY
RNU ± TEMPLETE LYMPHADENCECTOMY
RECURRENCE
MINIMAL INVASIVE / OPEN (cT3 ± cN+)
CLOSE AND STRINGENT FOLLOW UP
SINGLE POST OPERATIVE DOSE OF INTRAVESICAL CHEMOTHERAPY

Fig. 5 Algorithm for the management of UTUC

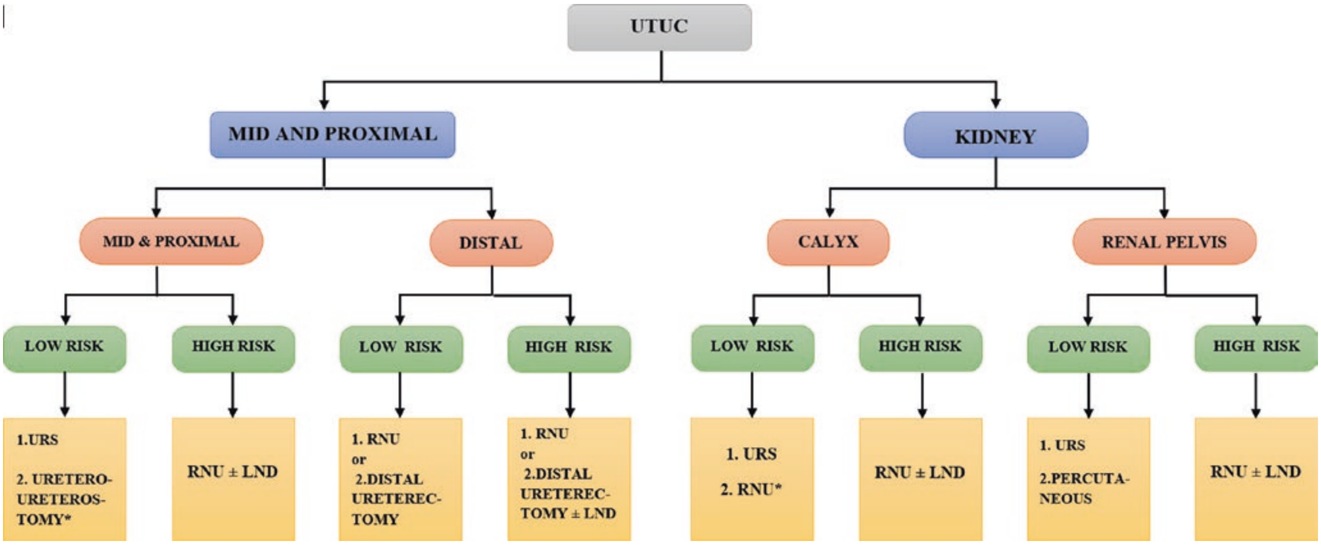

UTUC
MID AND PROXIMAL
KIDNEY
MID & PROXIMAL
DISTAL
CALYX
RENAL PELVIS
LOW RISK
HIGH RISK
LOW RISK
HIGH RISK
LOW RISK
HIGH RISK
LOW RISK
HIGH RISK
1.URS
2. URETERO-URETEROS-TOMY*
RNU ± LND
1. RNU or 2.DISTAL URETEREC-TOMY
1. RNU or 2.DISTAL URETEREC-TOMY ± LND
1. URS
2. RNU*
RNU ± LND
1. URS
2.PERCUTA-NEOUS
RNU ± LND

Fig. 6 Surgical treatment of UTUC according to location and risk status

Table 8 Stage-wise prognosis with current Rx [52]

Stage	5-year survival (%)
I	> 90
II	73
III	41
IV	< 20

10 Stage-Wise Prognosis with Current Rx (Table 8) [52]

11 Management of Recurrent Disease Including Specific Palliative Measures

The RNU alone is offered only in the palliative circumstance in patients with metastatic UTUC as there is no oncological advantage [53]. In selected metastatic UTUC patients who are fit to receive treatment, there is an overall survival advantage in combining chemotherapy and RNU vs. chemotherapy alone [54]. Recent trials of new immunotherapeutic drugs (PD1 inhibitors) have demonstrated a response in a proportion of patients with UTUCs; hence, they can be used for second-line treatment in metastatic UTUC; however, it still remains a challenge [55].

12 How We Do It at TMC

- Patients are referred to TMC for UTUC cancer based on radiological or endoscopic findings of mass in the upper tract.
- Based on available imaging, urine cytology is sent for all patients.
- Radiological evidence and cytology positivity are sufficient to prove the diagnosis of tumor.
- Biopsy (endoscopic/image-guided) is advised when radiological/cytological evidence is insufficient to prove the diagnosis.
- Histopathology reported elsewhere is reviewed by GU pathologist at TMC to confirm concordance of grade, depth and ruling out variant histology.
- Cystoscopic evaluation is done in all patients to rule synchronous bladder tumor.
- UTUC patients are categorized into low or high risk based on risk stratification suggested by the EAU guidelines.
- All low-risk tumors are managed conservatively.
- Radical nephroureterectomy with bladder cuff excision with template lymphadenectomy is the treatment of choice for all high-risk patients except when preservation of renal function is a goal. It is performed either open or minimally invasive technique (laparoscopic/robotic).
- Perioperative single intravesical instillation of Mitomycin-C is done in all patients undergoing radical nephroureterectomy.
- Adjuvant treatment is considered in high-grade and high-risk patients.
- Surveillance of all patients is done as per EAU guidelines.
- Patients with metastatic disease are considered for palliative chemotherapy, pain management, nephrostomy, angioembolization and palliative radiotherapy based on their presentation and performance status.

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Prostate Cancer

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Abbreviations

ADT	Androgen-deprivation therapy
ART	Adjuvant radiotherapy
AS	Active surveillance
BPH	Benign prostatic hypertrophy/hyperplasia
CRPC	Castrate-resistant prostate cancer
CT	Computed tomography
DRE	Digital rectal examination
EBRT	External beam radiation therapy
EFS	Event-free survival
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
GS	Gleason score
HIFU	High-frequency ultrasound
IGRT	Image-guided RT
IMRT	Intensity-modulated RT
LRP	Laproscopic radical prostatectomy
LUTS	Lower urinary tract symptoms
mCRPC	Metastatic castration-resistant prostate cancer
ORP	Open radical prostatectomy
OS	Overall survival
PARP	Polyadenosine diphosphate-ribose polymerase
PSA	Prostate-specific antigen
RARP	Robotic radical prostatectomy
RFA	Radiofrequency ablation
rPFS	Radiographic progression-free survival
RT	Radiotherapy
SBRT	Stereotactic body radiotherapy
SRT	Salvage radiotherapy 3D-CRT three-dimensional conformal RT
VMAT	Volumetric-modulated arc therapy
WW	Watchful waiting

1 Epidemiology

- Second most common malignancy in men after lung cancer.
- Incidence variable across countries due to differences in implementation of screening.
- Higher prevalence in the West.
- GLOBOCAN 2018 data [1]: 7.1% of all new cancers worldwide (1.3 million cases) and 3.8% of all cancer related deaths (359,000 deaths).
- The age-adjusted deaths from prostate cancer have declined 51% from 1993 to 2014 [2].
- The decreasing and comparatively low death rate may be a result of increased public awareness leading to early detection and treatment.
- Both environmental and genetic factors play a role in pathogenesis.
- Age, race and family history are important risk factors.
- Risk of prostate cancer in first-degree relatives is twofold higher than general population.
- Additionally, if prostate cancer is diagnosed in men <60 years of age, this risk increases by fourfold.
- Genomic studies have reported 77 SNPs associated with prostate cancer [3].
- BRCA 2 mutations are important mutations increasing risk by 5- to sevenfold.
- Other mutations/genes implicated are CHEK2, PALB2, BRIP1 and NBS1.
- Molecular classification emerging to streamline treatment guidelines.

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2 Clinical Features [2, 4]

The clinical manifestations of prostate cancer often mimic those of benign prostatic hypertrophy/hyperplasia (BPH) which is more common than prostatic cancer. Both conditions often coexist in elderly males. Careful history and physical examination can provide clues towards making a correct diagnosis in most cases.

2.1 Symptoms

In the West, most patients are asymptomatic and report to their heath caregivers with raised or abnormal PSA levels. However, in developing countries including India, symptoms of metastatic disease, bladder outlet obstruction and haematuria are common presentations.

The symptomatology of prostate cancer can be divided as:

1. *Asymptomatic*: Most men with early stage prostate cancer may have no symptoms attributable to the cancer.
2. *Local symptoms*: Include *low back ache, lower urinary tract symptoms (LUTS)* due to an enlarged prostate, *erectile dysfunction, hematuria* and *hematospermia*. An overlapping problem of coexisting urinary tract irritation/infection can mislead the clinician. Symptoms of urinary frequency, urgency, nocturia and hesitancy are often related to a concomitant BPH. Hematuria and hematospermia though uncommon, their presence in older men should raise the suspicion of prostate cancer. Erectile dysfunction is considered to be a late symptom and is due to invasion of the neurovascular bundles.
3. *Symptoms due to metastases*: *Bone pain* due to bony metastases is the commonest symptom. Others include *cough, breathlessness, haemoptysis* and *abdominal pain* due to hepatomegaly. Occasional patients can also present with *palpable masses, lymphedema* or *venous thromboembolism* secondary to nodal enlargement.
4. *Acute symptoms: Acute urinary retention, massive haematuria* or *pathological fractures* including *spinal cord compression and symptoms related to hypercalcaemia* can be found.

2.2 Clinical Examination

General physical examination may reveal *pallor, supraclavicular adenopathy, hepatomegaly, ascites* and *pedal oedema.*

Digital rectal examination (DRE): Presence of asymmetric areas of induration or nodules suggests cancer. Patients with an abnormal DRE irrespective of serum PSA levels warrant further evaluation in the form of prostatic biopsy. DRE detects tumours in the posterior and lateral aspects of the gland. However, tumours in other parts or small tumours may be missed on DRE. The PPV for malignancy with an abnormal DRE is around 12%.

3 Evaluation of Prostate Cancer [5]

The evaluation of prostate cancer complements a good history taking and physical examination with special emphasis on digital rectal examination for prostate assessment.

3.1 Serum PSA

- Serine protease (glycoprotein) secreted by prostatic epithelium.
- Produced by the action of Human Kallikrein-2 enzyme on the precursor ProPSA.
- Normally present in semen and serves to cleave and liquefy seminal coagulum.
- Normal value: <4 ng/mL with $t^{1/2}$ of 2.2 days.
- Two forms: Free PSA and bound PSA (alpha 1-antichymotrypsin (90%)/alpha 2-macroglobulin).
- Increase in PSA: Due to disruption of cellular architecture within prostate; seen in prostate cancer, prostatitis, BPH, following prostate biopsy, prostatic infarction, recent sexual activity, following TURP (PSA is thus organ but not cancer specific).
- Decrease in PSA: following hormonal therapy.
- A value of >10 ng/mL has a 67% probability of cancer. Thirty percent of men with high PSA will have prostate cancer. PPV of PSA is 25–40%. Generally, patients with prostate cancer will have values >20 ng/mL.
- Uses: Detection of primary/recurrent tumours; during follow-up; tool for screening along with DRE.
- Types
  - (a) *PSA density*: Defined as serum PSA/volume of prostate gland. Normal value is <0.15. It has a sensitivity of 75% and specificity of 44% in diagnosis.
  - (b) *PSA velocity*: Defined as rate of change of PSA. An increase of 0.75 ng/mL/year increases cancer risk. Rapid PSA doubling is associated with increased treatment failure rates and increase in cancer related mortality.
  - (c) *Complexed PSA*: Defined as ratio of free PSA/total PSA.
  - (d) *PSA density of transitional zone*: Defined as ratio of serum PSA to volume of transitional zone.
  - (e) *% Free PSA*: Defined as free PSA/total PSA X 100. A lower value (<10%) indicates cancer while a value >25% implies no risk. It is valuable when serum PSA is 4–10 ng/mL (borderline) and there is history of previous negative biopsy.

3.2 TRUS

- One of the most accurate method for local staging in prostate cancer.
- Besides obtaining biopsy, it is also used for screening, for measurement of prostate volume, to assess prostate blood flow and in brachytherapy/cryotherapy of gland.
- Probe frequency is 7 MHz.
- Prostate cancers appear as hypoechoic nodules (60–70% cases). Extra-capsular spread is suggested by identifying a bulge in the prostate contour and an angulated appearance of lateral margin. Seminal vesicle involvement is denoted by bulge at the base of the seminal vesicle and altered echogenicity.
- D/Ds of hypoechoic nodules include infarcts, granulomas and lymphomas.
- Advantages: Cost effective, no risk of radiation and day care procedure.

3.3 Prostate Biopsy

- Indications: a) Palpable masses on DRE (abnormal DRE); b) elevated PSA; c) both elevated PSA with abnormal DRE.
- Types: (a) *Sextent* (6 cores): Higher false negativity of 15–34%; (b) *extended* (10–12 cores): Increases detection rate and current gold standard; (c) *saturation* (18–21 cores): Increases detection rate and also detection of insignificant (low grade) prostate cancers. It is used when primary biopsy is negative and involves biopsy of the prostatic apex.
- Methods: a) *TRUS guided;* b) *transperineal*: A reduction in risk of sepsis (<1%) but an increase in urinary retention (2%–9%); c) m,*ultiparametric MRI guided*: Useful for patients undergoing repeat biopsy (increases detection in up to 54% cases) and improves sampling rates and d) *MRI/TRUS fusion biopsy.*
- Gun used: *End fire sampling* tend to have better detection rates compared to *Side fire sampling* in retrospective studies. However, RCTs show no difference.
- Complications: (a) Bleeding (1%–4%); (b) infections (0.1%–7%); (c) UTI (2%–6%); (d) urinary retention (1%) and (e) vasovagal attack (1.4%–5.3%).
- Implications:
  - HGPIN on biopsy: No immediate treatment needed; repeat biopsy after 3 years.
  - Multifocal HGPIN: Doubles risk of cancer; repeat biopsy within first year.
  - Adenocarcinoma: Stage and treat accordingly based on Gleason score, PSA.
- Repeat biopsy: Performed when a) raising PSA with initial negative biopsy; b) persistently elevated PSA; c) abnormal histologies like ASAP; d) % free PSA < 10% and e) inadequate initial biopsy. A repeat biopsy increases cancer detection by 16%–40%.
- Gleason score: Most common system used for grading prostate cancer. It is based on glandular pattern at low magnification and degree of glandular differentiation. Grading occurs from 1 to 5 where 1 indicates well differentiation and 5 poorly differentiated cancers. Based on the grade, a Gleason score (GS) is calculated using the dominant grade identified + next dominant grade present. Therefore, GS varies from 2 to 10. A tertiary GS is one in which a high-grade minor component is also added to the score. Poorly differentiated tumours have a GS: 8–10 while well-differentiated tumours have a GS: 2–4.

3.4 PSMA PETCT

- Staging modality for prostate cancer especially for intermediate and high-risk prostate cancers by offering ‘one stop shop’ for staging by demonstrating local infiltration, lymphatic spread and distant metastases.
- PSMA: Prostate-specific membrane antigen is a 750 amino acid trans-membrane protein located within the apical epithelium of secretory ducts of normal prostate tissue.
- In malignancy, PSMA expression in elevated in tumour tissues compared to benign prostatic hyperplasia/enlargement which show no increased uptake. This increased expression correlates with Gleason score and PSA levels.
- Provides additional molecular information on disease distribution over and above standard imaging.
- In patients with biochemical recurrences, PSMA can help distinguish local recurrence or nodal metastases, even when PSA levels are low.
- PSMA PET is better than conventional bone scans for detecting bone metastases.
- *Theranostic application* by linking PSMA antibodies to radio-ligands to facilitate elective irradiation.
- Overall sensitivity is fairly moderate (33%–66%) but specificity is excellent (98%–100%).
- PSMA is not prostate specific: Physiological uptake occurs in kidney, salivary glands, small bowel, spleen and liver. It can also be expressed by other tumours like gastric, colorectal, breast and renal cancers.
- Recent meta-analysis of 1309 patients evaluated in16 studies failed to make any form of conclusive recommendations for use in staging [6].
- PSMA negative prostate cancers, micrometastases are common causes of false-negative results.
- Ubiquitous availability of these scans is still a realization.

3.5 FDG PETCT

- As an alternative for staging when PSMA PETCT scans not available.
- FDG uptake correlates with more aggressive tumours with poorly differentiated histologies.
- May be less sensitive for detection of bony metastases as PETCT picks up lytic lesions better than sclerotic lesions.
- Lower sensitivity compared to PSMA PETCT.

3.6 Tc^{99}Bone Scan

- Tc^{99}-MDP (Technetium methylene diphosphonate) bone scan is still the standard of care for evaluation of bony metastases.
- Usually indicated when PSA > 20 ng/mL, presence of bony symptoms or locally advanced disease (cT3/T4).
- Increased uptake correlates with osteoblastic activity: Feature of prostate cancer metastases (>80%).
- Higher false positives: Degenerative bony diseases, inflammation and fracture sites.

3.7 MRI Pelvis

- Prostate cancer appears as reduced signal intensity in the peripheral zone on T2W images.
- Improves local staging by depicting adjacent soft tissue involvement.
- Accuracy of staging varies from 51% to 92%.
- Relatively expensive, operator dependent and difficult to perform biopsies.
- Multiparametric MRI: Combines T2W imaging with diffusion weighted imaging and MR spectroscopy. It helps increasing detection rates.

3.8 CT Scan

- Features of malignancy include obliteration of periprostatic fat planes, abnormal enhancement of contiguous NVB and extension into adjacent organs.
- Demonstrates bladder/rectal invasion, lymphadenopathy and distant metastases.
- Can be used to obtain FNAC from lymph nodes increasing accuracy.

3.9 Blood Investigations

- Complete hemogram: May demonstrate a) anaemia due to chronic hematuria/secondary to renal failure/leucoerythroblastic anaemia; b) leukopenia due to leucoerythroblastic anaemia and c) thrombocytopenia due to DIC/bone marrow invasion.
- Liver function tests: May be abnormal due to extensive liver infiltration.
- Renal function tests: May show azotaemia due to bilateral ureteric obstruction secondary to trigonal involvement or due to extensive retroperitoneal nodes causing ureteric compression.

3.10 Prostascint

- Form of radio immunoscintigraphy: Murine monoclonal antibody to the intracellular component of PSMA conjugated with Indium (In^{111}) is infused into patients. SPECT images are then taken to depict uptake at various sites.
- Relatively expensive and cumbersome and not routinely used.

4 Screening

- Important because most prostate cancers are indolent in nature; as a result, the majority of patients die with prostate cancer rather than from it.
- Important because treatment-related morbidity and side effects impair the quality of life of these patients in the long run.
- Therefore, a screening program which can accurately pick up asymptomatic men with aggressive localized tumours which can contribute to prostate cancer-related mortality and be diagnosed early and treated.
- PSA has been used as a marker for screening.
- The European Randomized Study of Screening for Prostate Cancer (ERSPC) Trial [7] reported an absolute survival benefit (albeit small) with PSA screening at 9 years of follow-up.
- The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial [8] found no benefit with combined annual PSA and digital rectal examination screening after 7–10 years of follow-up.
- Conflicting trial results have made screening in prostate cancer a controversial topic.
- Although screening with PSA can reduce cancer-specific mortality, the absolute risk reduction is small.
- The benefits of screening being outweighed by the potential harms including the substantial risk of over-diagnosis need to be kept in mind before undertaking screening.
- In India, opportunistic screening in which PSA is undertaken in patients who visit the health care provider is followed.

- Thorough discussion with the patient important in this regard before initiation of screening.
- US Preventive Task Force (USPTF) 2017 guidelines [9]: For men above 70 years, no PSA-based screening is recommended (category D) and for men between the ages of 55–69 years, PSA-based screening must be individualized (Category C recommendation).

5 Principles of Treatment

5.1 Localized Prostate Cancer

- Disease confined within the gland with no extra prostatic extension or distant metastases which includes T1-T2c, N0 and M0 cancers.
- Treated with curative intent.
- T1 cancers: Diagnosed incidentally on TURP specimens undertaken for coexisting BPH.
- Patient with good PS and life expectancy of >/= 10 years, radical prostatectomy remains the treatment of choice.
- Patient is unfit or is unwilling for surgery, radical radiotherapy is used.
- Active surveillance is an option in patients who are compliant for follow-up and have cancers fitting into the Epstein criteria (very low risk tumours) with a life expectancy of 10 years or more.

5.2 Locally Advanced Prostate Cancer

- Cancer outside the prostate gland but confined to the pelvis with no distant metastases.
- Includes T3-T4a, N0-N1 tumours.
- Multimodality treatment is necessary.
- Options include
  - RP followed by RT + HT.
  - NAHT followed by RT + HT.
- Neoadjuvant hormonal therapy reduces the tumour burden and helps achieve negative margins, given for 6 months prior to definitive treatment and continued for 2–3 years.
- Nodal disease must be addressed appropriately.
- Active surveillance is not an option in these patients.

5.3 Metastatic Prostate Cancer

- Includes cancers with distant nodal and/or visceral metastases.
- The performance status of patient, life expectancy, site and volume of disease: Important factors for consideration of treatment.
- Patients with poor PS and low life expectancy: ‘Watchful Waiting’ where symptomatic treatment is initiated only when symptoms appear.
- Combination of chemotherapy and hormonal therapy (chemo-hormonal therapy) is used.
- Chemotherapy is important in those with high volume of disease burden especially visceral metastases. Agents include docetaxel, abiraterone, etc.
- Abiraterone is used as frontline therapy for patients without visceral metastases.
- Hormonal therapy includes surgical (bilateral orchiectomy) or medical castration (GNRH analogues [agonists/antagonists] or anti-androgens).
- Surgical castration is cheaper, one-time treatment, irreversible but may have psychological effects on the patient.
- GNRH analogues are administered every 3–6 monthly lifelong. They are more expensive.
- Anti-androgens (e.g. bicalutamide) are oral formulations that are administered along with surgical castration.
- Hormonal therapy causes cardiac problems, osteoporosis with prolonged usage.

5.4 Castrate-Resistant Prostate Cancer (CRPC)

- Cancers which are not hormonally sensitive.
- Resistance occurs due to various mechanisms.
- Treatment involves use of chemotherapy, ketoconazole, immunotherapy and oestrogens.
- Associated with prostate cancer related mortality.

6 Radical Prostatectomy [4]

Radical prostatectomy is the oldest curative treatment for prostate cancer and remains a ‘gold standard’ modality because:

- Hormonal or chemotherapy are never curative,
- Radiotherapy or other physical forms of energy may not completely eradicate all cancer cells, even in a gland contained cancer.

6.1 Indications

- Patients with cT2 or lower cancers.
- High risk localized prostate cancer defined by PSA>/= 20 OR Gleason score >/= 8 OR clinical stage T of >/= 3a.

Patients must have a life expectancy of at least 10 years. The tumour should be biologically significant and completely resectable. The accepted upper age limit to undertake the surgery is about 75 years.

6.2 Methods/Types

6.2.1 Open Radical Prostatectomy

- e. Retropubic prostatectomy: This technique was first propounded by Millin in 1947. Generally, this approach is adopted due to familiar surgical anatomy; lower risk of rectal injury and postoperative faecal incontinence, wider exposure and access for performing pelvic lymphadenectomy, preservation of the neurovascular bundles and lesser risk of positive margins. However, it is associated with increased blood loss, impotence and urinary incontinence.
- Perineal prostatectomy: Associated with less blood loss and shorter operative time than the retropubic approach. The potential disadvantages are poor access for performing a pelvic lymphadenectomy, higher rate of rectal injuries and occasional postoperative faecal incontinence. It is also more difficult to preserve the cavernosal nerves with this approach.

6.2.2 Laparoscopic Radical Prostatectomy

It is associated with less bleeding and post-operative pain, better visualization and shorter recovery time. Performed through transperitoneal or extraperitoneal approaches. Transperitoneal approach facilitates lymphadenectomy but has a higher risk of adjacent intestinal and vascular injury, urinary leaks and postoperative bowel obstruction. Haemostasis in the neurovascular bundles is difficult due the relative difficulty in the placement of haemostatic sutures/clips. Additionally, heat from the cautery can irreversibly damage them. The rates of positive margins have been reported higher and oncological adequacy remains to be proven.

6.2.3 Robotic/Robotic-Assisted Radical Prostatectomy

Associated with greater technical ease, especially for suturing the vesico-urethral anastomosis. It is less invasive and associated with lower pain and a quicker recovery. Cost can be a deterrent for usage. The only phase III randomized trial comparing robotic with open prostatectomy was conducted in Australia and found no difference in oncological and functional outcome of the two techniques at a follow-up of 24 months [10]. A recent Cochrane review that compared either robotic radical prostatectomy (RARP) or laparoscopic RP (LRP) vs. open radical prostatectomy (ORP) included two RCTs. The main conclusions were that there were no significant differences between the comparisons for oncological, urinary function and sexual function outcomes, although the minimally invasive techniques were associated with a statistically significant improvement in duration of hospital stay and blood transfusion rates over open RP. Thus, there is no recommendation of surgical approach of one over the other [11].

6.2.4 Salvage Prostatectomy

Performed in patients where local treatments have failed. It is associated with higher and more serious complications that are much more difficult to manage.

6.3 Main Steps of Prostatectomy

- Opening of the endopelvic fascia and limited incision of the puboprostatic ligaments.
- Suture ligation and transection of Santorini’s dorsal venous complex.
- Dissection of urethra at the prostatic apex and urethral transection.
- Dissection of the prostate from the neurovascular bundles.
- Transection of the prostatic pedicles.
- Transection and reconstruction of the neck of the bladder.
- Dissection of seminal vesicles and vas deferens.
- Performance of vesicourethral anastomosis.
- Pelvic lymphadenectomy.

6.4 Post-Operative Care

- Catheter removal 3 to 21 days after surgery. Removal of the catheter before 7 days is associated with a 15% to 20% risk of urinary retention.
- Kegel’s exercises.
- Protective pads or diapers may be used until complete urinary control is achieved.
- Postoperative serum PSA levels should be undetectable by 30 days after surgery.

6.5 Complications

- *Early*: Haemorrhage; adjacent structure (rectal, vascular, ureteral or nerve) injuries; urinary leak/fistula formation; thromboembolic and cardiovascular events; urinary tract infection; lymphocoele and wound infection.
- *Late*: Erectile dysfunction, urinary incontinence and urethral strictures.

6.6 Contraindications

Mainly for minimally invasive techniques and include:

- *Absolute*: Uncorrectable coagulopathies, inability to undergo general anaesthesia.
- *Relative*: Prior lower abdominal/pelvic surgery, morbid obesity, large prostate size (e.g. >100 g), prior pelvic irradiation or prior prostate surgery.

6.7 Adjuvant Therapy after Surgery

- *Node negative*: Adjuvant radiotherapy for pT3 tumours and margin positivity. However, survival advantage may not be significantly different compared to salvage radiotherapy at biochemical recurrence.
- *Node positive*: Androgen-deprivation therapy (ADT), either immediate or delayed, leads to improvement in disease free and overall survival. Use of adjuvant radiotherapy remains controversial.

6.8 Evidence

- Scandinavian trial [12]: At a median follow-up of 13 years, patients who underwent radical prostatectomy had a reduction in cancer-related mortality (RR: 0.56 and absolute risk difference of 11%) compared to those undergoing watchful waiting in the study that included 695 men.
- PIVOT (Prostate Cancer Intervention Versus Observation Trial) [13]: Showed survival benefit in those with high-risk features (e.g. PSA>/= 10) on subset analysis.
- SWOG 8794 trial [14]: Adjuvant RT improved OS and metastases-free survival in patients with margin positive or pT3 disease.
- EORTC 22911 trial [15]: Improved biochemical-free survival and reduction in local recurrence in patients >70 years old or those with positive margins.

6.9 Advantages

- Possibility of cure with minimal surgical trauma to surrounding tissues.
- Accurate tumour staging for planning further treatment.
- Treatment failure easily identified by PSA estimation during follow-up.
- Relatively smooth postoperative course, short hospital stay and very low post-operative mortality.
- Reduction in disease progression locally as well as reduction in the risk of distant metastases, thus improving cancer-specific and overall survival.
- Recurrences can be salvaged by radiotherapy.

6.10 Disadvantages

- Possibility of incomplete resection of the tumour.
- Risk of erectile dysfunction and urinary incontinence are comparatively lesser with use of nerve sparing techniques.

7 Active Surveillance (as) [16]

7.1 Definition

This includes observation rather than immediate therapy, with curative intent treatment deferred until there is evidence that such patients are at increased risk of disease progression.

7.2 Rationale

- Carcinoma prostate is often detected when it is not clinically evident.
- Indolent cancers can often be differentiated from aggressive ones by clinico-pathological parameters.
- Any form of definitive treatment is always associated with appreciable side effects and costs.
- By adopting surveillance, those patients who are at high risk of disease progression receive definitive therapy.
- Thereby, quality of life remains unaffected in majority of patients which becomes an important parameter in younger patients with respect to voiding and sexual disturbances.

7.3 Indications

AS is applicable to most men with Gleason 6 cancer; also, selected patients with Gleason score (GS): 3 + 4 with a low percentage of component 4 may be candidates for active surveillance. Patients with a life expectancy of >10 years are offered AS. There is no lower age limit for AS.

7.4 Components of AS

7.4.1 Selection of Patients Who Are at Low Risk of Disease Progression

- Many clinico-pathological criteria exist to select these patients.
- These criteria include early clinical stages, low PSA levels and a GS consistent with a well-differentiated cancer.

Some of them also include number of positive biopsy cores and percentage of positive cores, PSA density and PSA kinetics to select patients.
- Endo-rectal MRI can often be used as a complementary tool to improve patient selection by increasing the accuracy and yield of prostatic biopsies. MRI has a 93% sensitivity in this regard.
- All patients must be adequately counselled regarding the treatment strategy and need to adhere for stringent follow-up.

7.4.2 Surveillance Strategy

- Patients are followed with serial PSA and repeat biopsies.
- Initial confirmatory biopsy is performed at 6–12 months, mainly targeting those prostatic zones that may be underevaluated during initial biopsy. Twenty-five to 3 percent of these patients may have a higher tumour grade which could have been missed during the initial biopsy. The basic premise of this confirmatory biopsy is to evaluate presence of higher grade tumour which makes patients unsuitable for active surveillance.
- A routine strategy includes half-yearly PSA, yearly DRE and a repeat biopsy with or without imaging at 3–5-year intervals.
- The interval between tests depends on patient's underlying risk factors and concern/anxiety regarding cancer spread.
- Five alpha reductase inhibitors (e.g. dutasteride) are being used to prevent or delay disease progression in patients managed under active surveillance.

7.4.3 Criteria for Switching from AS to Definitive Treatment

- When repeat biopsy shows Gleason 4/5.
- Increase in either the number of positive cores or percentage of positive cores on biopsy.

7.5 Guidelines

The guidelines from important associations have been listed in Table 1.

7.6 Outcomes

- PIVOT trial [13]: Lack of survival benefit of immediate surgery compared to observation alone at 12 years.
- ProtecT trial [20]: Compared AS with radical prostatectomy and radical radiotherapy for localized prostate cancer. This included 82,429 men and the primary end point was prostate cancer specific mortality at 10 years. This trial showed no difference is mortality among the 3 arms. However, both the surgery and radiotherapy arms were associated with lower disease progression and development of metastatic disease.

7.7 Advantages

- About two-thirds of early stage cancer patients will avoid treatment.
- Side effects of treatment is reduced.
- Quality of life remains unaffected.
- Reduces the need for treating small, indolent cancers.

7.8 Disadvantages

- Can lead to psychological harm and unfound anxiety in patients.
- Increased risk of erectile dysfunction in those undergoing repeat biopsies.
- About one-third of patients will eventually require treatment, although there may be no impact on cure rates.

Table 1 Guidelines for active surveillance from various international associations

Guidelines	Low risk	Intermediate risk	Tests	Other tests
ASCO[17] (2016)	AS preferred	Active treatment; AS for selected patients	PSA q3–6 months DRE q1 year Biopsy: within 6–12 months, then q3–5 yearly	MRI investigational
AUA[18] (2017)	Same	AS for selected patients	Same	Same
NICE[19] (2016)	Same	Radical treatment	PSA q3–4 months, monitor kinetics; rest same	MRI at enrolment

ASCO American Society of Clinical Oncology, *AUA* American Urological Association, *NICE* National Institute for Health and Care Excellence, *AS* active surveillance, *DRE* digital rectal examination

Table 2 Important trials for active surveillance in prostate cancer

Study	n	Follow-up (median) (in years)	Freedom from treatment	No biochemical evidence of disease	Prostate cancer mortality	OS
UCSF [21]	321	3.6	67%@5 years	1 recurrence at 3 years	0	0
University Toronto [22]	993	8.5	70%@5 years	47%: at 5 years	5% @ 15 years	10 year OS: 68%
PRIAS [23]	2494	1.6	77% @2 years	–	0	4 year OS: 87%
University of Miami [24]	230	2.6	85.7% @ 5 years	0	0	–
John Hopkins [25]	1298	5	59% @ 5 years	90.6% at 2 years	0.1% at 15 years	15 year OS: 69%
Royal Marsden [26]	471	5.7	70% @ 5 years	85% at 5 years	2% at 8 years	8 year OS: 9%

OS overall survival, *UCSF* University of California, San Francisco, *PRIAS* Prostate Cancer Research International Active Surveillance

7.9 Evidence

Nine prospective studies which include around 10,000 men have been published. The largest and most mature data is shown in Table 2.

The limitation of most of these studies is that the follow-up period is relatively small.

An important term to be differentiated is ‘watchful waiting’ (WW). In WW, monitoring continues until patient develops symptoms when palliative androgen-deprivation therapy is instituted. This method is adopted for patients who have a life expectancy of less than 10 years. This could be applied to all prostate cancer patients irrespective of cancer stage.

8 Focal Ablation [27, 28]

Focal ablation is a form of local therapy to treat localized prostate cancer.

8.1 Rationale

The lesion with the largest and highest grade (in the setting of multifocal disease) serves as the driver for clinical progression of disease. By ablating this index lesion, disease progression can be delayed or stopped. Use of multiparametric MRI can confidently target suspicious lesions for biopsy and hence ablation.

8.2 Indications

Indicated for small (at least 0.5 m^3 with a maximum core length of >/= 6 mm of cancerous tissue) or any sized lesion with Gleason 4 or more.

8.3 Contraindications

- Those with contraindications to MRI (pacemaker, aneurysmal clips, etc.)
- Allergic to MRI contrast.
- Significant CKD precluding contrast use.
- Those with clinically insignificant disease of size less than 0.5 mm^3 or low Gleason score (</= 3).

8.4 Methods

Ablation can be performed by various techniques that include high-frequency ultrasound (HIFU), cryoablation, laser ablation, photodynamic therapy, focal brachytherapy, radiofrequency ablation (RFA) and irreversible electroporation. Candidates are selected using template mapping or multiparametric MRI-based biopsies to appropriately identify these lesions. Treatment techniques include targeted focal ablation, hemiablation and hockey stick patterns (anterior and posterior). Lesions which are not clinically significant must not be targeted.

8.5 Follow-Up and Outcome Assessment

- Disease recurrence is assessed using biopsies which are performed in view of raising PSA, suspicious MRI or both.
- Biopsy must be 4–6 targeted cores from margins of zone of ablation which included at least 1 sample from ablated zone.
- Follow-up MRI must be done 6–12 months after procedure to identify failure or recurrence.
- Treatment may include reablation, active surveillance of whole gland therapy.

8.6 Advantages

- Offers good oncological outcomes with low complication rates.
- Healthy gland is preserved and minimizes risk of damage to adjacent structures.
- Performed as a day care procedure.

9 Radiotherapy

For men with localized prostate cancer, external beam radiation therapy (EBRT) along with androgen-deprivation therapy (ADT) has become the standard definitive treatment option for with long-term control outcomes comparable to surgery [21]. Improvements using cross-sectional imaging for treatment planning [29] and intensity-modulated radiotherapy [30] with daily image guidance [31] have permitted accurate delivery of radiation to the target.

The sensitivity to fractionation of irradiated tissue is characterized by a parameter called the α/β ratio. The α/β ratio of adenocarcinoma prostate is low, in the range of 1–2Gy [32–34]. The α/β ratio of the adjacent rectum is greater than that of prostate cancer [35, 36], implying that hypofractionation may further improve the therapeutic ratio of EBRT.

9.1 Definitions

A recent publication by Morgan et al. [37] has defined the following schedules.

Type	Fraction size (Gy)
Conventional	1.8–2
Moderate hypofractionation	2.4–3.4
Ultra-hypofractionation	≥ 5

The fraction size gap created by definitions (3.4-5Gy) represents a relatively little studied range.

9.2 EBRT Techniques

The prostate, rectum and bladder are delineated on axial pelvic computed tomography (CT) images. Treatment planning algorithms then calculate the dose and the beam arrangements are planned to the target volume.

- Three-dimensional conformal RT (3D-CRT).
- Intensity-modulated RT (IMRT)—Delivers non-uniform beam intensities with dose escalation. Volumetric-modulated arc therapy (VMAT) is an evolution of IMRT with a circular technique of radiation delivery.
- Image-guided RT (IGRT)—Technique acquiring 2D/3D images prior to each treatment providing accurate localization of the prostate, which varies daily due to bladder and rectum filling, e.g. gold marker (fiducial) tracking with megavoltage imaging, kilo-voltage (kV) imaging, abdominal ultrasound or CBCT.
- Stereotactic body RT (SBRT)—Alternative for selected men with low to intermediate risk.
- Proton beam RT—Majority of the energy is deposited in the region of the Bragg peak, beyond which the dose sharply falls to zero.
- Carbon ion RT—Being evaluated, primarily in Japan, as an alternative form of particle irradiation.

Gold Standard for EBRT—IMRT with IGRT

9.3 Indications

- Definitive radiotherapy
- Adjuvant radiotherapy
- Salvage radiotherapy
- Hypofractionation

10 Definitive Radiotherapy

10.1 Low Risk

The ProtecT [19] trial randomized 1643 patients to active treatment (RP/EBRT) and Active Surveillance which confirmed that RT plus 6 months of ADT improved PFS but not OS. If RT is performed in this group, dose escalated IMRT (74-80Gy) alone, or moderate hypofractionation should be used. LDR brachytherapy is an alternative.

10.2 Intermediate Risk

IMRT with short-term ADT (4–6 months) can be used to treat such patients suitable for ADT [38–40]. For unsuitable patients or unwilling for ADT, the recommendation is dose escalated IMRT/VMAT with or without brachytherapy. HDR brachytherapy alone is a valid treatment option for select patients conferring 5-year PSA control >90%, with minimal (<5%) late Grade 3+ GU and GI toxicity [41, 42].

10.3 High Risk

Dose escalated IMRT/VMAT and long-term ADT is the preferred approach as per current recommendation. The role of pelvic radiation is being evaluated in recent trials.

Table 3 Trials for androgen depravation therapy with radiotherapy in locally advanced prostate cancer

Study	n	Median F/U(yr)	Randomization	Outcomes
Intergroup T94–0110[44]	1205 (1057 with T3–4 disease)	8	ADT vs. ADT + RT (65-69Gy) ADT: Lifelong LHRH agonist or bilateral orchiectomy	10 year OS: 45% vs. 55% ($I = 0.001$)
RTOG 85–31[45]	945 [T3 (82%) or N1(18%)]	7.6	RT vs. RT + ADT(44–46Gy to whole pelvis; 20–25Gy boost to prostate) ADT: Goserelin at least 2 years, preferably until progression	10 year OS: 39% vs. 49%, ($p = 0.002$) 10 year DSS: 78% vs 84%, ($p = 0.005$) OS benefit limited to patients with Gleason 7–10
EORTC 22961[46]	970 (T2c-T4 or N1–2)	6.4	RT + ADT for 6 months vs. RT + ADT for 36 months (prostate dose: 70Gy) ADT: 6 months CAB (LHRH agonist + anti-androgen) ± 2.5 years LHRH agonist	5 year OS: 81% vs. 85% ($p = 0.02$) 5 year DSS: 95% vs. 97% ($p = 0.002$)
DART 01/05 Spain [47]	355 (47% IR, 53% HR)	5.3	RT + ADT for 4 months vs. RT + ADT for 28 months (prostate dose:76–82Gy) ADT: Goserelin + anti-androgen for 4 months total (prior to andduring RT) ±2 years Goserelin	5 year OS: 86% vs. 95% ($p = 0.009$) 5 year BRFS: 81% vs. 89% ($p = 0.019$) 5 year metastasis-free survival: 83% vs. 94% ($p = 0.009$)

IR intermediate risk, *HR* high risk, *ADT* androgen deprivation therapy, *BRFS* biochemical recurrence-free survival, *OS* overall survival, *DSS* disease-specific survival, *CAB* complete androgen blockade, *LHRH* luteinizing hormone-releasing hormone

10.4 LDR Brachytherapy Boost

ASCENDE-RT [43] Trial compared dose escalated EBRT (46Gy) and LDR brachytherapy to EBRT (78Gy) in intermediate- and high-risk patients showing 5 and 7 years PFS (89% and 86% vs. 84% and 75%, respectively) increase at the cost of late Grade 3+ urinary toxicity (18% vs. 8%).

10.5 Locally Advanced/Very High Risk/Regional

No standard treatment is defined. Randomized trials have established long-term ADT with RT providing better OS than either ADT or RT alone (Table 3).

Subgroup analysis from RTOG 85-31 showed that 95/173 pN1 patients treated with pelvic RT with immediate ADT had better 5-year (54%) and 9-year (10%) PFS rates compared to RT alone ($p < 0.0001$). Multivariate analysis revealed a statistically significant effect on OS [48]. Similar results have been confirmed from the control arm of the STAMPEDE trial in a non-randomized comparison [49].

11 Adjuvant Radiotherapy

Three prospective trials have assessed the role (Table 4).

Table 4 Trials for adjuvant radiotherapy in prostate cancer

Study	n	Inclusion criteria	Randomization	Definition of BCR PSA (ng/mL)	Median F/U (yr)	Biochemical PFS	OS
SWOG 8794[50]	431	pT3cN0 ± involved margins	60–64Gy vs. Observation	> 0.4	12.6	10 year: 53% vs. 30% ($p < 0.05$)	10 year:74% vs. 66% ($p = 0.023$)
EORTC 22911[15]	1005	pT3 ± involved margins pN0; pT2 involved margins pN0	60Gy vs. Observation	> 0.2	10.5	10 year: 60.6% vs. 41% ($p < 0.001$)	10 year: 81% vs. 77% (NS)
ARO 9602[51]	388	pT3 (± involved margins) pN0; PSA post-RP undetectable	60Gy vs. Observation	> 0.05 + confirmation	9.3	10 year: 56% vs. 35% ($p = 0.0001$)	10 year: 82% vs. 86% (NS)

SWOG South West Oncology Group, *EORTC* European Organization for Research and Treatment of Cancer, *NS* not significant, *PFS* progression-free survival, *OS* overall survival

Table 5 Trials for salvage radiotherapy in prostate cancer

Study	n	Risk groups	Median F/U (mo)	Randomization	Outcome
GETUG AFU16[52]	369 RT+ ADT vs. 374 RT	GS ≤ 7 (89%) GS ≥ 8 (11%) cN0	63	66Gy + GnRH X 6 months vs. 66Gy	5 year PFS: 80% vs. 62% ($p < 0.0001$)
RTOG 9601[53]	384 RT + ADT vs. 376 RT	pT2 R1, pT3 cN0	156	64.8Gy + bicalutamide X 24 months vs. 64.8Gy + placebo	12 year DM: 14% vs 23% ($p = 0.005$) 12 year OS: 76% vs 71% ($p = 0.04$)

ADT androgen depravation therapy, *GS* Gleason score, *GnRH* gonadotropin-releasing hormone, *PFS* progression-free survival, *DM* distant metastases, *OS* overall survival, *mo* months

12 Salvage Radiotherapy (SRT)

PSA failure may occur in 15% to 40% of patients after RP. Salvage RT is usually combined with hormonal therapy (Table 5).

12.1 Artistic Meta-Analysis Presented at the ESMO Congress 2019

Across three trials (RADICALS, RAVES, GETUG AFU 17), 1074 men were randomized to adjuvant radiotherapy and 1077 to salvage radiotherapy. Adjuvant RT (ART) did not improve event-free survival (EFS) compared to early salvage RT with a 1% difference in EFS at 5 years. More than 60% of men randomized to eSRT in these trials are yet to start RT. The role for ART in some men from subgroup analyses is yet to be determined [54].

13 Hypofractionation Radiotherapy (HFX)

13.1 Moderate Hypofractionation

Meta-analysis reveals dose escalation (74–80Gy) is associated with higher late GI toxicity compared to lower doses (64–70.2Gy) [55]. Another meta-analysis of 25 studies including >14,000 patients concluded that HFX could be more effective than conventional fractionation [33] as it is more convenient for the patient and economical for the health care system (Table 6).

The CHHiP Trial [56] consolidates the role of moderate hypofractionation as the new standard of care in the treatment of prostate cancer in the UK.

Presently, in North America, NCCN [2] considers moderate hypofractionation using IMRT “an alternative to conventionally fractionated regimens when clinically indicated.”

The AUA/ASTRO/ASCO group recommends moderate HFX for localized prostate cancer patient (of any risk category) as the evidence is strong for its use in the clinics [60].

13.2 Ultra-Hypofractionation (SBRT)

Katz et al. [61] showed that SBRT to a dose of 35–36.25Gy treated with Cyber knife in five daily fractions in early low-risk prostate cancer provides acceptable outcomes and toxicity. Though there is no data presently to suggest benefit to escalation beyond 35Gy. Ten-year BDFS seems higher than with standard IMRT. Scandinavian HYPO-RT-PC [62] trial done for the intermediate risk group presented in ESRTO 37, Barcelona (full publication awaited) seems to be beneficial as well. Trials are on-going in high-risk disease. The recom-

Table 6 Trials for hypofractionated radiotherapy in prostate cancer

Study	n	Median F/U (yr)	Study arms	Technique	Risk groups	ADT	Outcome	Toxicity
CHHiP [56]	3216	5.2	*CRT*—74Gy/37# *HFX*—SSSSSS60Gy/20#, 57Gy/19#	IMRT IGRT optional (53% use)	LR:15% IR: 73% HR:12%	97%	HFX non-inferior	NS
HYPRO [57]	820	5	*CRT*—78Gy/39# *HFX*—64.6Gy/19#	IMRT,IGRT	IR: 26% HR:74%	67%	Not significant	Favors CRT
PROFIT [58]	608	6	*CRT*—78Gy/39# *HFX*—60Gy/20#	3D CRT or IMRT,IGRT	IR: 100%	None	HFX non-inferior	NS
RTOG 0415 [59]	1115	5.8	*CRT*—73.8Gy/41# *HFX*—70Gy/28#	3D CRT or IMRT,IGRT	LR: 100%	None	HFX non-inferior	NS

CRT conventional radiotherapy, *HFX* hypofractionated radiotherapy, *NS* not significant, *IMRT* intensity-modulated radiotherapy, *IGRT* image-guided radiotherapy, *3DCRT* 3D conformal radiotherapy, *LR* low risk, *IR* intermediate risk, *HR* high risk, *Gy* Gray; # fractionation, *ADT* androgen depravation therapy

mendation for use of ultra-hypofractionated EBRT in low risk and intermediate risk is graded as "conditional" in the literature reflecting only moderate-quality evidence. With any hypofractionated approach, IGRT is strongly recommended.

13.3 Complications

- Gastrointestinal—Acute toxicity: Proctitis (5%–30%), enteritis, urgency, tenesmus. Resolves within 3–8 weeks. Late toxicity: Persistent diarrhea, rectal urgency or hematochezia. Incidence ≥ Grade 3 toxicity ranges from 1% to 5% [63–65].
- Genitourinary – Acute toxicity: frequency, dysuria, urgency due to cystitis, urethritis or both [63–65]. Resolves within 4 weeks. Late toxicity (uncommon): Urethral strictures, cystitis, hematuria and bladder contracture.
- Sexual dysfunction – In contemporary series, 30%–45% of men become impotent after therapy, with incidence increasing over time [66, 67].
- Insufficiency fractures – physiologic stress to weakened bone.
- Secondary malignancy – Small increase in the incidence of bladder and rectal cancer, with the risk of mortality at 10–15 years being miniscule [68, 69].

14 Chemotherapy

14.1 Metastatic Disease

14.1.1 Castration/Hormone-Sensitive Prostate Cancer (CSPC/HSPC)

Testosterone serves as the main stimulant for prostate cancer growth [70, 71]. Androgen-deprivation therapy (ADT), which is the gold standard for the initial systemic treatment of metastatic prostate cancer, lowers the serum testosterone levels to castration levels. ADT can be achieved with either surgical or medical orchiectomy.

Surgical Orchiectomy

Bilateral orchiectomy rapidly decreases serum testosterone to castrate levels. It is a relatively simple, cost-effective procedure [72]. It is also advantageous in patients in whom a rapid fall in testosterone is indicated in patients with urinary tract outlet obstruction or in impending spinal cord compression. Another important factor for men choosing between surgery and medical treatment is the psychological impact which surgical castration may have. Placement of testicular prostheses or a subcapsular orchiectomy may decrease the psychological effects [73].

Medical Orchiectomy

Medical orchiectomy through its effects on the hypothalamic–pituitary axis decreases testicular production of testosterone. Medical orchiectomy can be achieved by gonadotropin-releasing hormone (GnRH) agonist or GnRH antagonist [74].

GnRH Agonists: GnRH agonists are agents that bind to the GnRH receptors on pituitary gonadotropin-producing cells, causing an initial release of both LH and follicle-stimulating hormone (FSH), causing the testicular Leydig cells to increase the testosterone production. The increased testosterone production causes a 'flare' of disease especially spinal cord compression and urinary tract obstruction [75]. Anti-androgens (Bicalutamide) are combined with GnRH agonists for 2–3 weeks to prevent the flare phenomeneon. GnRH receptors are down regulated after a week [76] and subsequently serum testosterone levels are reduced after 3–4 weeks [77]. Leuprolide, goserlein, buserlein and triptorelin are the GnRH agonists available for use.

GnRH Antagonists: GnRH antagonists (e.g. degarelix) suppress the testosterone levels while avoiding the flare phenomenon. GnRH antagonists like the agonist too bind to the

GnRH receptors on pituitary gonadotropin-producing cells but do not stimulate an initial release of LH or FSH.

14.2 Combinations with Anti-Androgen Therapy

- Docetaxel
- Abiraterone
- Apalutamide
- Enzalutamide

14.3 ADT plus Docetaxel

- There are 3 large RCTs which compared ADT alone as the standard of care with ADT combined with docetaxel (75 mg/sq.m, every 3 weeks) (within 3 months of ADT initiation) along with pre-medicated steroid therapy. Overall survival was the primary objective in all three studies.
- The Chemo-hormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (*CHAARTED*) randomized 790 patients with mHSPC to receive either ADT + docetaxel (75 mg/m^2 every 3 weeks for six cycles) (ADT-DOCE) or ADT alone. The median overall survival was 13.6 months longer with ADT-DOCE than with ADT alone (57.6 months vs. 44.0 months; HR 0.61; 95%CI 0.47–0.80) at a median follow-up of 28.9 months. Other endpoint of study, median time to biochemical, symptomatic, or radiographic progression was 20.2 months in the ADT-DOCE group, as compared to 11.7 months in the ADT-alone group (HR 0.61, 95%CI 0.51–0.72). In a subgroup analysis of patients, the overall survival was increased (51.2 vs. 34.4 months; HR, 0.63; 95% CI, 0.50–0.79; $P < 0.001$) in patients with high-volume disease (defined as presence of visceral metastases or ≥ 4 bone lesions, with ≥1 beyond the vertebral body or pelvis), whereas there was no improvement in OS (63.5 vs. not reached; HR, 1.04; 95% CI, 0.70–1.55; $P = 0.86$) in patients with low-volume disease [78]. In the updated analysis of the trial at a median follow-up 53.7 months, the median OS was 57.6 months for the ADT-Doce group versus 47.2 months for ADT alone (HR,0.72:95%CI,0.59 to 0.89, $p = 0.0018$) Patients with high-volume disease had an OS benefit of 17 months (51.2 v/s 34.4,HR,0.63,95% CI,0.50 to 0.79, $p < 0.001$), while those with low-volume disease did not have an OS benefit (HR, 1.04, 95%CI, 0.70 to 1.55, $p = 0.86$) [79].
- *STAMPEDE* trial [49] is a multiarm, multistage design. Totally, 2962 patients were randomized in 2:1:1:1 ratio into 4 arms—(SOC; ADT alone), SOC + zoledronic acid (SOC + ZA), SOC + docetaxel (ADT-DOCE) or SOC with both zoledronic acid and docetaxel (SOC + ZA + Doc). The patient population comprised 697 (24%) men who were N0M0, 448 (15%) with N+/X M0 and 1817 (61%) men with M+ disease. At the median follow-up of 43 months (IQR 30–60), ADT-DOCE arm showed significant improvement in survival compared with ADT 81 months v/s 71 months (HR 0.78, 95%CI 0.66–0.93), ZA showed no evidence of survival improvement and addition of ZA to ADT-DOCE did not show any overall survival benefit. ZA should not be part of standard of care for this population was the conclusion of this trial. An updated analysis of STAMPEDE recently published, suggest that after median follow-up of 6 years, among 1086 M1 patients, 468 (56%) had high and 362 (44%) had low metastatic burden. There is affirmative evidence of benefit of docetaxel over SOC on OS (HR = 0.81, 95% CI 0.69–0.95, $P = 0.009$) with no evidence of heterogeneity of docetaxel effect between metastatic burden sub-groups (interaction $P = 0.827$). Evidence of benefit was found after analysing other outcomes for docetaxel over SOC in failure-free survival (HR = 0.66, 95% CI 0.57–0.76, $P < 0.001$) and progression-free survival (HR = 0.69, 95% CI 0.59–0.81, $P < 0.001$) with no evidence of heterogeneity of docetaxel effect. The clinically significant benefit in survival for upfront docetaxel persists even after longer follow-up, with no evidence that benefit differed by metastatic burden. STAMPEDE group concluded regardless of metastatic burden in patients with metastatic hormone naïve prostate cancer patients' upfront docetaxel should be considered [80].
- In the *GETUG 15 trial* [81], a total of 385 patients were randomized to ADT or ADT plus Docetaxel. At a median follow-up of 84 months, overall survival was increased in the chemo hormonal arm, but the difference was not statistically significant (62 months vs. 49 months, HR088, 95% CI, 0.68 to 1.14).
- In all three trials, toxicity was mainly haematological, Grade 3–4 neutropenia being around 12%–15% and Grade 3–4 febrile neutropenia around 6%–12%. Febrile neutropenia shows significant reduction by use of granulocyte colony-stimulating factor receptor (GCSF) [82, 83]. Based on these data, docetaxel combined with ADT should be considered as a standard in men presenting with metastases at first visit, provided they are fit enough to receive the drug [49, 78, 81].

14.4 ADT plus Abiraterone

LATITUDE Trial [84] randomized 1199 men with newly diagnosed castration sensitive to ADT plus abiraterone and prednisone or to ADT plus matching placebos. Patients had high-risk disease with the presence of at least two out of three high-risk parameters: Gleason score 8 or higher, at least three bone lesions and the presence of measurable visceral metastasis. At a median follow-up of 52 months, overall survival was significantly increased with the addition of abiraterone plus prednisone (median survival not reached versus 34.7 months, hazard ratio [HR] 0.62, 95% CI 0.51–0.76). Abiraterone arm had higher incidence of grade3 or more hypertension and hypokalemia.

STAMPEDETrial [49]: One thousand nine hundred and seventeen men were randomly assigned to ADT plus abiraterone and prednisone or to ADT alone. The overall survival was significantly increased with the addition of abiraterone (3-year survival 83 versus 76% with ADT alone, HR 0.63, 95% CI 0.52–0.76). The failure-free survival was also significantly increased in the ADT plus abiraterone arm of the trial (3-year failure-free survival rate 75 versus 45, HR 0.29, 95% CI 0.25–0.34).

14.5 ADT plus Enzalutamide

ENZAMET(ANZUP 1304) [85]: Phase III trial randomized standard-of-care therapy with or without enzalutamide for metastatic hormone-sensitive prostate cancer (mHSPC). In total, 1125 patients were randomized to receive ADT plus either ENZA or NSAA (NSAA: bicalutamide, nilutamide or flutamide) with or without docetaxel. The overall survival was significantly prolonged in the enzalutamide arm compared to the non-steroidal anti-androgen arm (HR 0.67, 95% CI 0.52–0.86) after a median follow-up of 34-month. Concurrent enzalutamide and docetaxel had more toxicity, and this subgroup did not have survival benefit.

14.6 ADT plus Apalutamide

TITAN was phase 3, double-blind trial of 1052 metastatic, castration-sensitive prostate cancer patient who received either apalutamide (240 mg per day) or placebo, added to ADT. The primary end points were overall survival and radiographic progression-–free survival. At the first interim analysis with a median follow- up of 22.7 months, radiographic progression-free survival at 24 months was 68.2% in the apalutamide group and 47.5% in the placebo group (hazard ratio for radiographic progression or death, 0.48; 95% confidence interval [CI], 0.39 to 0.60; $P < 0.001$). The frequency of grade 3 or 4 adverse events was 40.8% in the placebo group, 42.2% in the apalutamide group and; rash was more common in the apalutamide group. Apalutamide was approved for treatment of metastatic castration-sensitive prostate cancer in the United States in September 2019 based on the TITAN trial [86].

14.6.1 Castration-Resistant Prostate Cancer (CRPC)

Definition

Disease progression on androgen-deprivation therapy (ADT) castrate serum testosterone <50 ng/dL or 1.7 nmol/L plus either

(a) Biochemical progression: Three consecutive rises in PSA 1 week apart resulting in two 50% increase over the nadir and a PSA > 2 ng/mL or,

(b) Radiological progression: The appearance of new lesions: Either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [87].

The pattern of disease includes non-metastatic (M0 with rising PSA and disease limited to prostate or metastatic (M1) which includes bone metastasis, nodal metastasis and visceral metastasis with or without bone metastasis.

14.7 Non-Metastatic CRPC

Apalutamide or enzalutamide are approved for non-metastatic CRPC.

Apalutamide: In a phase 3 SPARTAN trial,[88] 1207 patients of non-metastatic CRPC with a PSA doubling time ≤ 10 months were randomized in a 2:1 ratio to receive apalutamide (240 mg per day) or placebo. The primary end point was metastasis-free survival (MFS). At the time of planned primary analysis, MFS was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo group (hazard ratio for metastasis or death, 0.28; 95% confidence interval [CI], 0.23 to 0.35; $P < 0.001$). The rate of adverse events leading to discontinuation of the trial regimen was 10.6% in the apalutamide group and 7.0% in the placebo group.

Enzalutamide: In a phase 3 study (PROSPER), [82] 1401 patients with M0 CRPC with a PSA doubling time ≤ 10 months and PSA ≥2 ng/mL were randomized (2:1) to enzalutamide 160 mg per day or placebo. The median metastasis-free survival was 36.6 months in the enzalutamide group versus 14.7 months in the placebo group (hazard ratio for metastasis or death, 0.29; 95% confidence interval, 0.24 to 0.35; $P < 0.001$). Adverse events of grade 3 or higher occurred in 31% of the patients receiving enzalutamide as compared with 23% of those receiving placebo.

14.8 Metastatic CRPC

In metastatic CRPC, multiple agents have shown benefit in addition to continued ADT:

- Next-generation antiandrogens.
- Chemotherapy.
- Immunotherapy.
- Bone-targeted agents.
- PARPi in men with DNA mismatch repair mutation.

14.8.1 Abiraterone

Chemotherapy-Naive

Abiraterone was evaluated in chemo-naïve 1088, asymptomatic or mildly symptomatic CRPC patients in the phase III trial COU-AA-302. Patients were randomized to abiraterone or placebo, both combined with prednisone (5 mg twice daily). Radiographic PFS (rPFS) and overall survival were the co-primary endpoints. After a median follow-up of 22.2 months, there was significant improvement of rPFS (median 16.5 vs. 8.2 months, HR: 0.52, $p < 0.001$). The OS endpoint was significantly positive (34.7 vs. 30.3 months, HR: 0.81, 95% CI: 0.70–0.93, $p = 0.0033$) at the final analysis with a median follow-up of 49.2 months. Adverse events (AEs) related to mineralocorticoid excess and liver function abnormalities were more frequent in abiraterone arm [83].

Post-Docetaxel

In a phase III trial (COU-AA-301), 1195 patients who had progression of disease over initial docetaxel received 1000 mg abiraterone plus prednisone or placebo. The median survival in the abiraterone group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, $p < 0.0001$) after a median follow-up of 20.2 months. The benefit was observed in all subgroups, and all the secondary objectives favoured abiraterone (PSA, radiologic tissue response, time to PSA or objective progression). Common Grade 3–4 AEs did not differ significantly between arms. As expected, mineralocorticoid-related side effects (fluid retention, oedema and hypokalaemia) were more frequent in the abiraterone group, and majority of SAE were mainly Grade 1–2 [89].

14.8.2 Enzalutamide

Chemotherapy naïve

A randomized phase III trial (PREVAIL) [90] compared enzalutamide and placebo in a chemo-naïve CRPC population of 1717 men and showed a significant improvement in both co-primary endpoints, rPFS (HR: 0.186; CI: 0.15–0.23, $p < 0.0001$) and OS (HR: 0.706; CI: 0.6–0.84, $p < 0.001$). The most common clinically relevant AEs were hypertension and fatigue.

Post-Docetaxel

In AFFIRM phase III trial of 1199 patients who had received prior docetaxel therapy was randomized 2:1 to enzalutamide 160 mg/day orally or placebo. The median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, $p < 0.001$) after a median follow-up of 14.4 months. The secondary endpoints QoL, time to PSA or objective progression, PSA reduction and soft tissue response favoured enzalutamide. Side effects were similar in both groups with only difference in seizure which was seen in 0.6% patients in enzalutamide arm [91].

14.8.3 Docetaxel

Docetaxel (75 mg/m^2) given every 3 weeks in combination with daily prednisone (5 mg twice a day) significantly prolonged overall survival compared with mitoxantrone plus prednisone in the TAX 327 phase III trial. 1006 men with mCRPC and good performance status were randomized to receive 5 mg prednisone twice daily and either docetaxel 75 mg/m^2 every 3 weeks; docetaxel 30 mg/m^2 weekly or; mitoxantrone 12 mg/m^2 weekly. The treatment was planned for up to 10 cycles of 3 weeks for the D3P arm and up to five cycles of 6 weeks for the D1P arm. Updated results showed a similar median survival benefit for docetaxel every 3 weeks v. mitoxantrone, with 3-year survival rates of 18.6% and 13.5%, respectively ($p = 0.005$). The magnitude of benefit associated with docetaxel plus prednisone treatment for CRPC was independent of age, performance status or baseline PSA [92].

14.8.4 Cabazitaxel

TROPIC trial was a phase III that compared cabazitaxel plus prednisone was to mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy. Patients received a maximum of ten cycles of cabazitaxel (25 mg/m^2) or mitoxantrone (12 mg/m^2) plus prednisone (10 mg/day). Overall survival was significantly longer with cabazitaxel (median: 15.1 vs. 12.7 months $p < 0.0001$) [93]. The PROSELICA trial evaluated two doses of cabazitaxel, 20 mg/m^2 versus 25 mg/m^2. It was a noninferiority trial. The lower dose was found to be noninferior and associated with fewer adverse events setting a new standard of care [94].

The CARD trial evaluated cabazitaxel in the third-line setting. Totally, 255 patients who had previously received docetaxel and an androgen-signaling-targeted inhibitor (abiraterone or enzalutamide) were randomized in 1:1 ratio to receive cabazitaxel (at a dose of 25 mg per square meter of body-surface area intravenously every 3 weeks, plus prednisone daily and granulocyte colony-stimulating factor) or the other androgen-signaling-targeted inhibitor (either 1000 mg of abiraterone plus prednisone daily or 160 mg of enzalutamide daily). The primary end point was imaging-based progression-free survival. Secondary end points of survival, response and safety were assessed. After a median follow-up of 9.2 months, the median imaging-based progression-free survival was 8.0 months with cabazitaxel and 3.7 months with the androgen-signaling-targeted inhibitor (HR, 0.54, 95% CI, 0.40 to 0.73; $p < 0.001$). Adverse events of grade 3 or higher occurred in 56.3% of patients receiving cabazitaxel and in 52.4% of those receiving an androgen-signaling-targeted inhibitor [95].

14.8.5 Sipuleucel-T

Sipuleucel-T is a dendritic cell vaccine that is prepared from peripheral blood mononuclear cells. A phase III trial tested Sipuleucel-T against placebo in 512 asymptomatic or minimally symptomatic CRPC patients where after a median follow-up of 34 months, and the median survival was 25.8 months in the Sipuleucel-T group compared to 21.7 months in the placebo group, with a HR of 0.78 ($p = 0.03$) [96].

14.8.6 Pembrolizumab

KEYNOTE-199 is a phase II trial that enrolled 255 patients with mCRPC treated with docetaxel and one or more targeted endocrine therapies in three cohorts. Cohorts 1 and 2 enrolled patients with RECIST-measurable PD-L1-positive and PD-L1-negative disease, respectively. Cohort 3 enrolled patients with bone-predominant disease, regardless of PD-L1 expression. All patients received pembrolizumab 200 mg every 3 weeks for up to 35 cycles. The primary end point was objective response rate. Pembrolizumab showed an objective response rate of 5% (95% CI, 2% to 11%) in cohorts 1 and 3% (95% CI, < 1% to 11%) in cohort 2. Treatment-related adverse events occurred in 60% of patients, were of grade 3 to 5 severity in 15% and led to discontinuation of treatment in 5% [97].

14.8.7 Radium-223

Radium-223 is a bone-targeted alpha-particle-emitting radioisotope. ALSYMPCIA is a phase III trial that tested Radium-223 against placebo in over 900 men with bone-predominant, symptomatic CRPC without visceral disease and no previous exposure of docetaxel. Radium-223 improved overall survival (HR 0.70; 95% CI 0.58–0.83) and time to first symptomatic skeletal event (HR 0.66; 95% CI 0.52–0.83) [98].

14.8.8 PARP Inhibitors

All men with metastatic prostate cancer should undergo germline testing and those with germline or somatic DNA repair mutation have an option of treatment with a poly-adenosine diphosphate-ribose polymerase (PARP inhibitor).

PRO found trial of randomized metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations in a 2:1 ratio to olaparib (300 mg bid) or the physician's choice of enzalutamide (160 mg/day) or abiraterone (1000 mg/day + prednisone 5 mg BID). The primary endpoint was radiographic progression-free survival (rPFS). Two hundred forty-five randomized to Cohort A. Olaparib was associated with improved rPFS compared to enzalutamide/abiraterone among patients in Cohort A (HR 0.34, 95% CI 0.25–0.47), which was consistent across the majority of subgroups assessed. The interim results for overall survival (OS) demonstrated improved survival among patients in Cohort A (HR 0.64, 95% CI 0.43–0.97) [99].

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Penile Cancer

Ganesh Bakshi and Mahendra Pal

Abbreviations

BXO	Balanitis Xerota obliterans
CRP	C-reactive protein
CT	Computerized tomography
DSNB	Dynamic sentinel lymph node biopsy
FDG	Fluorine 18 fluorodeoxyglucose
FNAC	Fine-needle aspiration cytology
HPV	Human papilloma virus
ILND	Inguinal lymph node dissection
LNM	Lymph node metastasis
LVI	Lymph vascular invasion
MILD	Modified inguinal lymph node dissection
MRI	Magnetic resonance imaging
PC	Papillary carcinoma
PeCa	Penile cancer
PET	Positron emission tomography
PLND	Pelvic lymph node dissection
PNI	Perineural invasion
RT	Radiation therapy
SCC	Squamous cell carcinomas
SCCAg	Squamous cell carcinoma antigen
VC	Verrucous carcinomas
VEIL	Video endoscopic inguinal lymphadenectomy

1 Introduction

Penile cancer (PeCa) is seen uncommonly in today's time in most parts of the world. It commonly affects poor socioeconomic group in developing countries. Many seek a delayed opinion in spite of noticing the lesion thereby leading to advanced disease at presentation. The treatment guidelines do not have many recommendations from randomized studies. Concerns regarding PeCa include delayed diagnosis, penile preservation, decisions in advanced disease, treatment related side-effects, and palliation.

2 Incidence and Epidemiology in India and Globally

The incidence in most part of the western world is decreasing in recent decades. The age-adjusted incidence is less than 1/100000 in Europe and North America, but in certain part of south America, Africa, and Asia, it is as high as 12/100000 [1]. In Europe, a recent review recorded the incidence of 0.58/100000 men. Brazilian cities of Sao Paulo and Recife have a higher incidence as well as Uganda [2, 3]. Lowest incidence has been in the Jewish community (0.1/100000) and may be due to the prenatal circumcision in Jews [4]. Low socioeconomic status and bad hygiene are associated with most cases [2, 4].

In India, PeCa account for approximately 1% of male cancers. It affects around 7% of men in the third decade and 19% in the fifth decade [2, 5, 6]. The disease is usually common in the fifth to seventh decades but occurs a decade or two earlier in developing nations [3].

2.1 Risk Factors and Premalignant Conditions

The risk factors strongly identified for PeCa are phimosis, chronic irritative and inflammatory condition such as balanitis Xerota obliterans (BXO) and balanoposthitis and association with human papilloma virus (HPV) 16 and 18 [7].

HPV association is present in more than 50% of cases with in situ, basaloid, verrucous penile carcinoma. Lichen sclerosus atrophus (also known as BXO) is associated with non-HPV PeCa [7]. Neonatal circumcision seems to have a protective role [8, 9]. Smegma was found to be carcinogenic in animal studies, but in human-related studies there is no relation with PeCa [10].

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Cigarette smoking is strong risk factor and has a 2.4–4.5 times the risk than nonsmokers and is directly proportional to number of cigarettes [11, 12].

Studies have been done about the relation of sexual relation with PeCa. Male partners of females with cervical intraepithelial neoplasia have a higher incidence of penile intra epithelial carcinoma. Also, males with early age of first intercourse and multiple sexual partners have a three- to five-fold increased risk [13].

HPV is known to alter the genomes thereby disturbing balance between oncogenes and tumor suppressor genes. There is 5-year survival advantage in PeCa associated with HPV DNA positive (78% vs. 93%, log rank test $P = 0.03$) [14]. There has also been an association between patients of condyloma acuminata and PeCa.

2.2 Premalignant Condition

Cuteneous horn, hyper keratotic dysplasia, giant condyloma (Buschke lowenstien tumor), pseudoepitheliomatosis, micaceous and keratotic balanitis, leukoplakia, BXO, and carcinoma in situ (Erythroplakia of Queyrat, Bowen's disease, and Bowenoid papulosis) are premalignant condition for PeCa [7, 15, 16].

3 Clinical Presentation in India and Globally

Patient with PeCa may present with localized, locally advanced or metastatic disease.

Patient may have phimosis and a lesion hidden below. In case it goes unnoticed, it can erode foreskin and grow further. Foul preputial odor and discharge with or without bleeding may be present.

Penile lesion may present in various forms—small papule, pustule and warty growth, and exophytic lesion, shallow or deeply excavated ulcer with elevated or rolled up edges (Fig. 1).

Inguinal mass, either enlarged or fungated nodes, may be another presentation. Occasionally, ulceration, suppuration, or hemorrhage is seen from nodal mass. Rare presentation would be urinary retention or urethral fistula.

Pain is not a presenting complaint. Weakness, weight loss, fatigue, and systemic malaise occur secondary to chronic suppuration or advanced disease. Because local disease and regional disease are usually far advanced by the time distant metastases occur, presenting symptoms referable to such metastases are rare.

In India,about three-fourths patients were older than 50 years. About 25% patients presented with phimosis and 20% patients had undergone circumcision after attaining adulthood.

Most patients presented with T2 disease, whereas palpable nodes, benign or malignant, were present in 55.5% and 76% patients in T1 and T2 patients, respectively [17].

Penile tumors occur most commonly on the glans (48%) and prepuce (21%) with involvement of glans and prepuce (9%), the coronal sulcus (6%), or the shaft (<2%) [18]. This distribution of lesions may be the result of constant exposure of the glans, coronal sulcus, and interior prepuce to irritants (e.g., smegma, HPV infection) within the preputial sac, whereas the shaft is relatively spared.

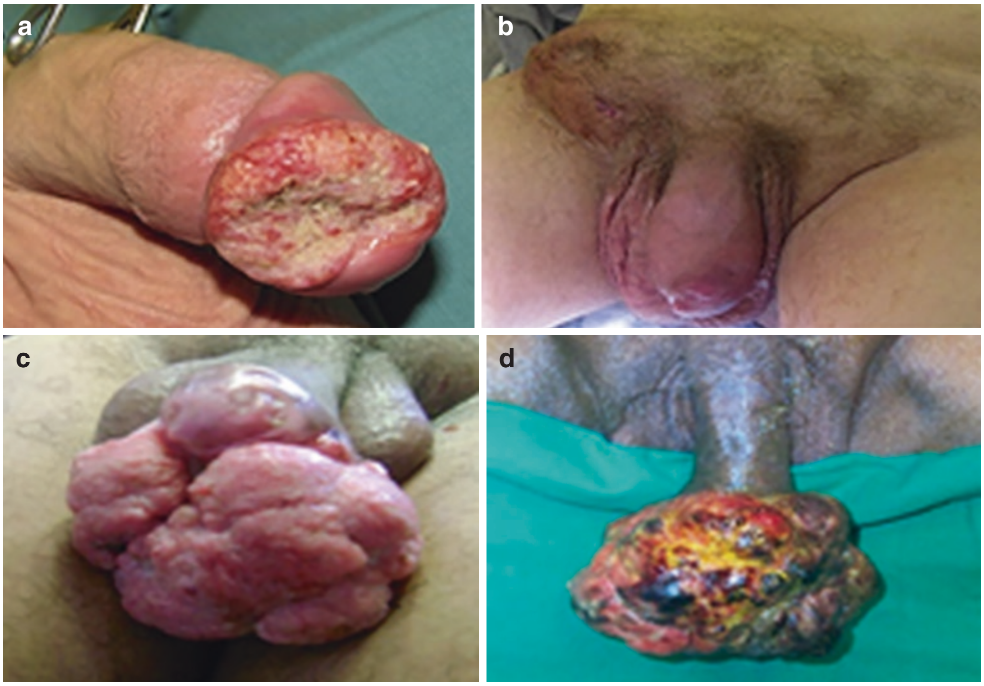

Fig. 1 (**a**–**d**) Penile lesions

4 Evaluation and Work-up

4.1 Diagnosis

1. Examination—Primary lesion described with respect to its site (preputial/penile shaft), appearance (verrucous/warty/ulcerative, invasive), size, and urethral/corporal involvement. Bilateral groin areas to be examined. Lymph nodes can be reactive in case of an infected penile lesion and at times they can be hard suggesting malignant spread [15].
2. Biopsy of penile lesion—Pathological diagnosis is mandatory.
3. Fine needle aspiration cytology (FNAC)—Cytology in enlarged or suspicious node or USG guided. High-frequency USG can help characterize nodes when indeterminate or in obese patients and also give information on pelvic nodes. It has a sensitivity of 39% and specificity of 100%. With significant false-negative rates, if FNAC is negative and clinical suspicion is high, a repeat FNAC or excisional biopsy can be done [19].
4. Magnetic resonance imaging (MRI)—In tumors extending on the root of penis, a good investigation for delineating extent and infiltration. Even gives better resolution of soft tissues and vasculature around enlarged nodes. MRI with lymphotropic nanoparticle (Ferrumoxtran-10) has shown a sensitivity of 100% and specificity of 97% in identifying occult metastases in a small series [20].
5. Computerized tomography (CT) scan—Usually done to assess lymph nodes.
6. Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) CT—Not routinely used, but has a good sensitivity ~90% and specificity ~100%, to Ca penis and its lymph node spread. In many small studies, it has been shown to be useful. PET CT has shown to be a promising investigation which can identify early metastases and is useful in following up groin of patients with Ca penis after primary treatment [21]. In patients with large palpable groin nodes, it can be a good investigation [22]. However, in patients with clinically normal groins, the sensitivity drops down to 20% [23].
7. Tumor markers—Biomarkers are used to estimate biological behavior [24], but rarely used due to suboptimal value. Currently, biomarkers do not have a routine place in current management of PeCa [25]. Available biomarkers are summarized below:
    (a) Plasmatic—Squamous cell carcinoma antigen (SCCAg) and C-reactive protein (CRP).
    (b) Proliferative—Ki-67 and proliferating cell nuclear antigen, HPV causes overexpression of E6 and E7 viral oncogenes, tumor suppressor gene TP53.
    (c) Cytogenetic—MYC gene and CDKN2A.

4.2 Pathology

Most primary malignant tumors of penis are squamous cell carcinomas (SCC) originating in the epithelium covering the glans, coronal sulcus, and inner foreskin. Glans tumors predominate over those exclusive of the foreskin or sulcus. Pathologically SCC may reveal varied patterns of growth like superficial spreading, vertical growth pattern, verruciform, and multicentric growth pattern. Of these, the vertical pattern has the most propensity to metastasize.

The various histologic subtypes seen in PeCa as below [26–30].

Squamous Cell Carcinoma: Most common, more than 70% cases. Microscopically, an infiltrating keratinized squamous carcinoma of moderate differentiation is noted.

Basaloid Carcinoma: Basaloid carcinoma is an aggressive, high-grade, and deeply invasive penile neoplasm, usually associated with HPV. More than half the patients have metastatic inguinal nodes at the time of diagnosis.

Verrucous Carcinomas (VC): VCs are slow-growing and grossly appear as exophytic, cauliflower like gray-white mass. The tumor can be locally aggressive, but it is biologically benign and should be treated accordingly.

Warty (Condylomatous) Carcinoma: Warty carcinomas are slow-growing, nonaggressive, verruciform HPV-related tumors.

Papillary Carcinoma (PC): PC is a type of low-grade verruciform carcinoma, lacking distinctive diagnostic features and having no association with HPV.

Sarcomatoid Carcinoma: Sarcomatoid carcinomas are rare, aggressive, large neoplasms predominantly composed of spindle cells.

Adenosquamous Carcinoma: Adenosquamous carcinoma is quite rare carcinoma which originates in misplaced glandular cells in the perimeatal region of the penis.

Carcinoma Cuniculatum: They are low-grade SCCs, which because of their "burrowing growth" are called as cuniculatum. Despite the deep penetration, none of the reported carcinoma cuniculatum cases showed groin or systemic metastases.

*Pseudohyperplastic Carcinom*a: It is a low-grade SCC preferentially affecting the foreskin of older patients in association with lichen sclerosus and usually they do not metastasize.

Acantholytic (Adenoid, Pseudoglandular) Carcinoma: These are high-grade, large, irregular masses involving multiple penile anatomical compartments and deeply invading having a higher incidence of regional metastases and mortality.

Clear Cell Variant of Penile Carcinoma: Very uncommon, linked with HPV, early metastasis, poor prognosis, lesion-dependent outcome, frequent lymphatic metastases—indicates a benefit of preventive lymphadenectomy for patients with clear-cell carcinomas [31].

Other Mixed Neoplasms: SCC can be found in association with any other subtypes of PeCa. Mixed carcinomas account for about 25% of PeCa.

5 TNM Staging of Penile Cancers [32]

The anatomic stage and prognostic groups stagings can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 706–707, Chapter no. 57, Penis, Table: Definition of TNM and AJCC prognostic stage groups and which can be accessed at https://www.pathologyoutlines.com/topic/penscrotumpenisstaging.html and https://www.cancerresearchuk.org/about-cancer/penile-cancer/stages-types-grades/tnm-staging

6 Principles of Management

The aim of treatment is first to take care of cancer as per oncological principles and secondly to try organ and functional preservation methods while being careful of the first aim. A safe surgical margin is necessary in case of surgical amputation. The earlier concept of a 2-cm margin has given way to around 1 cm margin. In patients where penile stump length is short, a margin lesser than 1 cm is acceptable, but these are tailor made decisions after due preoperative counseling of patient and his family. For a general recommendation, 3–5 mm can be considered safe maximum [33].

Stage of disease and presence of lymph node metastasis (LNM) remain the most important prognostic factors for disease outcome. Histological subtype, grade, perinodal extension, and lymphatic and/or venous embolization are the most important variables that predict inguinal LNM [34].

7 Surgical Management

For small lesions, less invasive surgery such as wide surgical excision with cold knife or CO2 laser, cryotherapy, radiation, Mohs's micrographic technique should be attempted. Other options include topical 5FU and 5% imiquimod applications and photodynamic therapy [35].

In preputial lesions either only circumcision or additional excision of part of glans penis might be required.

In slightly bigger lesions, a glansectomy or a partial amputation of penis would be necessary (Fig. 2). Even in partial penectomy, a good stump for sexual function and upright micturition should be achieved. In few cases, a total amputation of penis with a perineal urethrostomy is required (Fig. 3) [36].

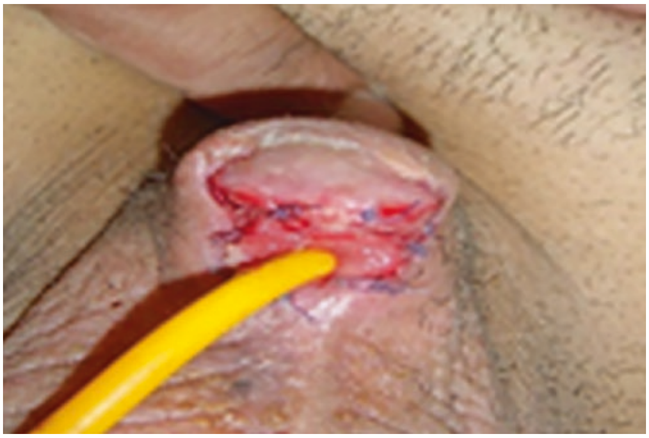

Fig. 2 Partial penectomy

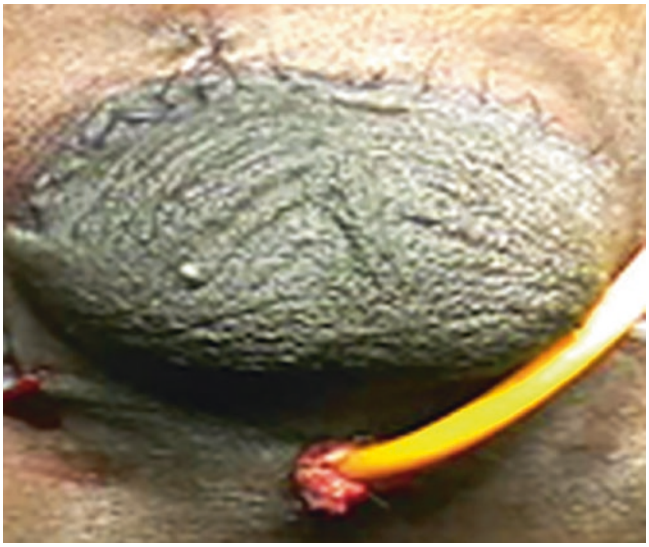

Fig. 3 Total penectomy with perineal urethrostomy

Generally, large widely infiltrative tumors have a poorer prognosis due to involvement of adjacent structures—lymphatics, lymphatic emboli, and involvement of vascular structures like corpora and blood vessels.

Radiation therapy should be given in few select patients with less than 4 cm superficial lesions with special techniques employed during the therapy. The complications include urethral stricture, penile necrosis, and recurrence [37].

8 Management of Lymph Nodes

20–25% of patients with clinically normal groins harbor occult metastases. In patients with palpable inguinal nodes, 70% of patients have metastases. In the remainder, nodes are enlarged due to infection. The traditional teaching of 6 weeks of antibiotics followed by reassessment of inguinal reassessment has been abandoned now to avoid a delay in diagnosis [38, 39].

8.1 Relevant Anatomy

Lymphatic drainage from penis parallels with superficial venous system that drains skin, glans and corporal bodies. The superficial inguinal nodes have been divided into five zones by drawing a horizontal and a vertical line through the point where the saphenous vein drains into the femoral vein with one zone directly overlying the junction. The smaller deep inguinal region is deep to the fascia lata along the medial aspect of the femoral vessels. Based on lymphangiographic studies, Cabanas described a sentinel lymph node located super medial to the epigastric-saphenous junction [40, 41].

Chaux et al. devised a prognostic index based upon histologic grade, extent and depth of tumor invasion, and perineural invasion. This group has proposed a scoring system to identify high risk patients likely to develop nodal metastasis in whom a prophylactic nodal dissection is advised [30].

If a malignant node is found on biopsy care should be taken to excise biopsy tract during subsequent lymphadenectomy [40].

8.2 Management of Patients with Clinically Normal Groin

Patients with clinically normal groins may harbor occult metastases in inguinal nodes. Risk stratification based on T stage and grade is an important tool to predict inguinal node involvement and survival in patients with clinically N0 inguinal nodes [42].

An optimum management strategy of these patients would be to offer early surgery and at the same time does not over treat patients unlikely to have nodal disease. Early surgical resection of inguinal nodes has therapeutic benefit. Inguinal lymph node dissection (ILND) has a reported complication rate ranging from 35 to 88%. So, patient selection is of prime importance when performing ILND in patients with clinically normal groins [43, 44].

In patients with clinically normal groins, three approaches of treatment are available. These are

1. Surveillance.
2. Dynamic sentinel lymph node biopsy (DSNB).
3. Modified inguinal lymph node dissection (MILD).

Risk-adapted approaches have been recommended by European Association of Urology to choose one or more of the above treatment options.

Surveillance can be offered to patients reliable for follow-up and with either low-risk or selected intermediate-risk patients.

8.3 Dynamic Sentinel Lymph Node Biopsy (DSNB)

The concept of sentinel node biopsy as proposed by Cabanas in 1977 initially was abandoned due to a large number of false negatives. This technique was revived later in 1992 by use of isosulphan blue dye as tracer and preoperative radioactive tracer (Technetium 99 m labeled nano colloid) in melanoma patients. Recently, with refinement of technique, a sensitivity of 93% and specificity of 100% has been reported from a two center prospective series of 323 patients. DSNB is recommended by European Association of Urology for all patients with intermediate or high-risk disease [45, 46].

8.4 Modified Inguinal Lymphadenectomy

MILD was first described in 1988 in an attempt to remove the nodes most likely to harbor tumor and to reduce the morbidity associated with complete inguinal node dissection. As originally described, this procedure consisted of a shorter skin incision, preservation of the subcutaneous tissue superficial to Scarpa's fascia, no dissection lateral to the femoral artery or caudal to the fossa ovalis, preservation of the saphenous vein, and elimination of Sartorius muscle transposition (Fig. 4). In a recent study evaluating follow-up (mean 78 months) of patients undergoing MILD, it was found that it has a significantly reduced complication rate compared to complete node dissection. However, despite a negative frozen section analysis bilaterally, 5.5% of inguinal regions were found to harbor occult metastases. Also, a minimum follow-up of 2 years following MILD has been sug-

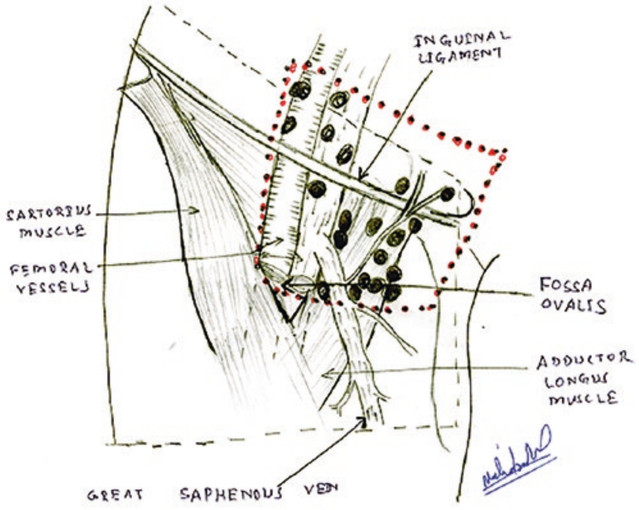

Fig. 4 Modified inguinal lymph nodes dissection boundaries

gested by the authors as all recurrences were within this period [47, 48].

8.5 Management of Patients with Node-Positive Disease

Complete ILND should be done if positive nodes are found on FNAC, excision biopsy, DSNB, or MILD. Complete ILND as described by Daseler is demarcated by four lines (Fig. 5).

Superior: from the anterior superior iliac spine to the external inguinal ring.

Lateral: From the anterior superior iliac spine extending 20 cm inferiorly.

Medial: From the pubic tubercle 15 cm inferiorly.

Inferior: Connecting the lower ends of the second and third lines.

The boundaries of dissection are as follows:

- Proximally: Inguinal ligament.
- Distally: Crossing of the Sartorius muscle and the adductor longus muscle (also referred to as the entrance of the Hunter canal, where the femoral vessels go under the muscles of the leg).
- Medially: Adductor muscle.
- Laterally: Sartorius muscle.

The floor of the dissection consists of the fascia lata, the femoral vessels, and the pectineus muscle.

The dissection should not be performed posterior to the vessels or around the femoral nerve. Sartorius muscle can be transposed medially to cover the femoral vessels.

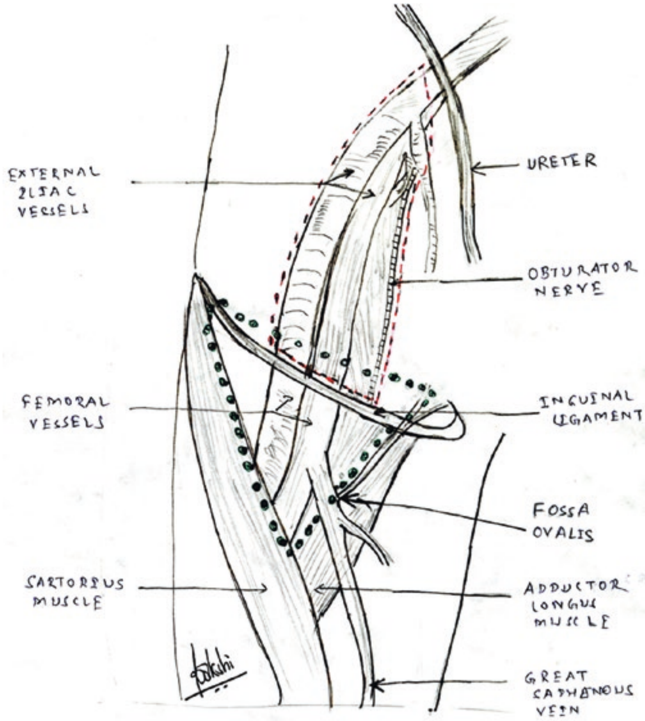

Fig. 5 Ilioinguinal lymph nodes dissection boundaries [1]. Deep inguinal lymph node dissection [2]. Pelvic lymph node dissection

8.6 Pelvic Lymph Node Dissection (PLND) [49]

Twenty to thirty percent of patients with positive inguinal nodes have positive pelvic nodes. An ipsilateral PLND of the affected site should be done in all patients with two or more inguinal nodes involved or with extranodal extension. Contra lateral PLND is not recommended in patients with unilateral nodal involvement as crossover from the groin to contralateral pelvic area is not known to happen. The boundaries of the PLND are as follows:

- Proximally: Common iliac vessels.
- Distally: The passage of lymphatic vessels to the groin,
- Laterally: Ilioinguinal nerve.
- Medially: Urinary bladder and prostate.
- Base: Deepest part of the obturator fossa.

8.6.1 Inguinal Wounds Post Groin Node Dissection

A primary closure if edges can be easily approximated after a Sartorius flip to cover vascular structures. If edges are under tension or apart, a pedicled anterolateral thigh flap is used to cover the defect.

8.7 Timing of Inguinal Lymphadenectomy

Inguinal lymphadenectomy (ILND) is known as early or prophylactic in CN0, generally within 6 weeks of treatment of primary and delayed or therapeutic when performed for development of palpable inguinal nodes during follow-up. Reviews of the published data showed a 5-year survival rate of 57–88% for early and 8–38% for delayed LND. Several investigators have concluded that delayed lymphadenectomy has a significantly decreased survival and is not recommended [50–52].

Whether ILND should be performed at same sitting as penectomy or after an interval of giving antibiotics had also been a subject of debate. Recent studies have failed to show any difference in operative morbidity if lymphadenectomy is done after 6 weeks of antibiotics hence it is suggested that inguinal lymphadenectomy can be done with primary surgery [53].

8.8 Complications of Inguinal Lymph Node Dissection

Complication rates ranging from 35 to 88% have been reported following ILND. Associated pelvic node dissection and use of radiotherapy have shown increased complication rates. Most common complications are wound infection with or without dehiscence (14 ± 50%), lymphocele/seroma (10 ± 10%), lymphedema, deep vein thrombosis, femoral neuropraxia, myocardial infarction, and rarely death [52].

8.9 Minimally Invasive Inguinal Lymphadenectomy

Video endoscopic inguinal lymphadenectomy (VEIL) has been tried in an attempt to reduce morbidity related to lymphadenectomy. In a recently published series of 33 VEIL performed in 20 men with a mean follow-up 20 months, the average operative time was 119 minutes and mean resected lymph nodes was 8 per lymphadenectomy. The overall complication rate was 33.2%. No patient had skin necrosis. The lymphatic complication rate was 27.2%.The overall survival rate was 80%, and cancer-specific survival was 90% [54]. Robotic VEIL is also described.

9 Medical Management

9.1 Chemotherapy

PeCa patients with large fixed, fungating, and sometimes fixed nodes are likely to have systemic disease, either occult or manifest. Surgery alone is not going to be curative and hence the role of multimodal treatment. Various drug combinations of cisplatin, fluoropyrimidines, gemcitabine, paclitaxel, bleomycin, methotrexate, and irinotectan have been put to use as neo adjuvant or adjuvant chemotherapy. Platinum-based chemotherapies have been the most active agents and have been always used in combinations. Earlier such studies had a survival of 3–11 months [55]. A response rate of 50% is achieved in neo adjuvant chemo therapy (NACT) with platinum combination therapies in fixed and locally unresectable groin nodes [56].

Adjuvant chemotherapy[AC] is given in pN2/pN3 patients and Pizzocaro et al. reported long-term disease-free survival(DFS) with AC than without AC in pN+ patients; 84% vs 39%.

5-Fluorouracil (5-FU) plus paclitaxel or docetaxel regime has shown a promising 52.6% DFS in median follow-up of 42 months. In patients with diagnosed PeCa metastases, prognosis is very poor but few series have reported a response rate of 30.8%. Chemo radiation is currently advised as a part experimental clinical scenario [57].

Avelumab (PDL1) and pembrolizumab (PD1) are being evaluated in 2 small phase II trials. TKI inhibitor dacomitinib has shown a response of 32% in similar circumstances. The results with these agents are quite promising [58].

The French study AFU-GETUG 25 (NCT02817958) is currently enrolling patients and aims to assess a multimodal approach for lymph node metastasis in penile SCCs—lymphadenectomy and adjuvant chemotherapy vs neoadjuvant chemotherapy followed by bilateral lymphadenectomy.

InPACT (NCT02305654) aims to determine prospectively the relative benefits and sequencing of surgery, chemotherapy, and chemoradiotherapy in the management of patients with penis cancer who present with palpable or radiologically evident inguinal lymph node metastases [59].

9.2 Radiation Therapy (RT)

9.2.1 RT for the Primary

Selected cases in PeCa, T1-2 lesions <4 cm, can be offered therapeutic radiation with the aim of cure and organ preservation. External RT of 60Gy using a penile mould, with brachytherapy (BT) boost or 55-60Gy dose in brachytherapy alone is used [60]. BT has good results reaching local cure rates of 90% with functional preservation and negligible morbidity [61].

A meta-analysis proved small benefit in favor of surgery than BT, 5 years OS being 76%vs 73%, and local cure rates of 84% vs 79% [62]. Glans necrosis, delayed corporal body fibrosis, urethral and meatal stenosis, and painful intercourse are some of the side effects of RT.

9.2.2 RT for Nodal Disease

RT to postoperative nodal regions is not suggested in pN_{2-3}. It can better the loco regional control of disease but with associated morbidity. Winters et al. also reported survival benefit with adjuvant RT [63]. In unresectable disease, it can be used as a method of palliation.

9.3 Role of Targeted Therapy

Anti-programmed death 1 (PD1), anti-PD-L1, and anticytotoxic T-lymphocyte antigen 4 (CTLA4) immunotherapy have emerged as a viable treatment option for a range of malignancies, including HPV-related neoplasms such as head and neck cancer.

Drug Avelumab—role in penile cancer patients—ongoing trials include the Phase II ALPACA trial (NCT03391479), which is actively enrolling patients with locally advanced or metastatic penile cancer who are ineligible for or progressing on platinum-based chemotherapy, and the (NCT03774901), which is looking into the role of avelumab as maintenance therapy after PR or stable disease with first-line chemotherapy.

NCT03686332 is a phase II research that compares the use of atezolizumab with or without radiation in individuals with advanced penis SCC, characterized as inoperable disease that is either locally progressed or metastatic. NCT04224740 is another phase II trial. Recruitment of patients with advanced illness to be given pembrolizumab in addition to standard-of-care treatment chemotherapy.

Multiple combination strategies with ICI are also being tested.

10 Stage-Wise Treatment Algorithms

10.1 Stage 1 and 2 Disease (Figs. 6 and 7)

10.2 Stage 3 Nodal disease—cN1, cN2 (Fig. 8). Treatment of Primary as in Stage 1 and 2 Disease

10.3 Stage 4 Disease—N3, T4, and M1 (Fig. 9)

10.4 Management of Recurrent Disease Including Specific Palliative Measures

In all recurrences or suspected recurrences, a biopsy or FNAC, appropriate imaging and good patient counselling, is to be done. In recurrence post penile conservative excision, are excision to achieve tumor-free status is needed—either a partial or total penectomy. If initial partial amputation, a total might be needed. In case of locally inoperable recurrences, neoadjuvant chemotherapy and reassessment for intervention are needed.

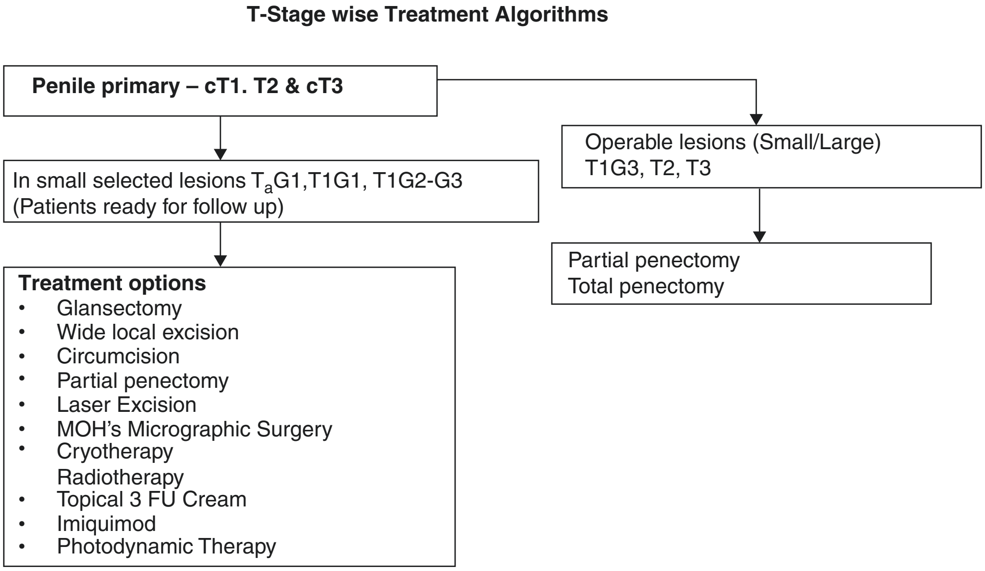
T-Stage wise Treatment Algorithms
Penile primary – cT1. T2 & cT3
In small selected lesions T_aG1,T1G1, T1G2-G3
(Patients ready for follow up)
Treatment options
• Glansectomy
• Wide local excision
• Circumcision
• Partial penectomy
• Laser Excision
• MOH's Micrographic Surgery
• Cryotherapy
Radiotherapy
• Topical 3 FU Cream
• Imiquimod
• Photodynamic Therapy
Operable lesions (Small/Large)
T1G3, T2, T3
Partial penectomy
Total penectomy

Fig. 6 Treatment algorithm for penile primary tumor

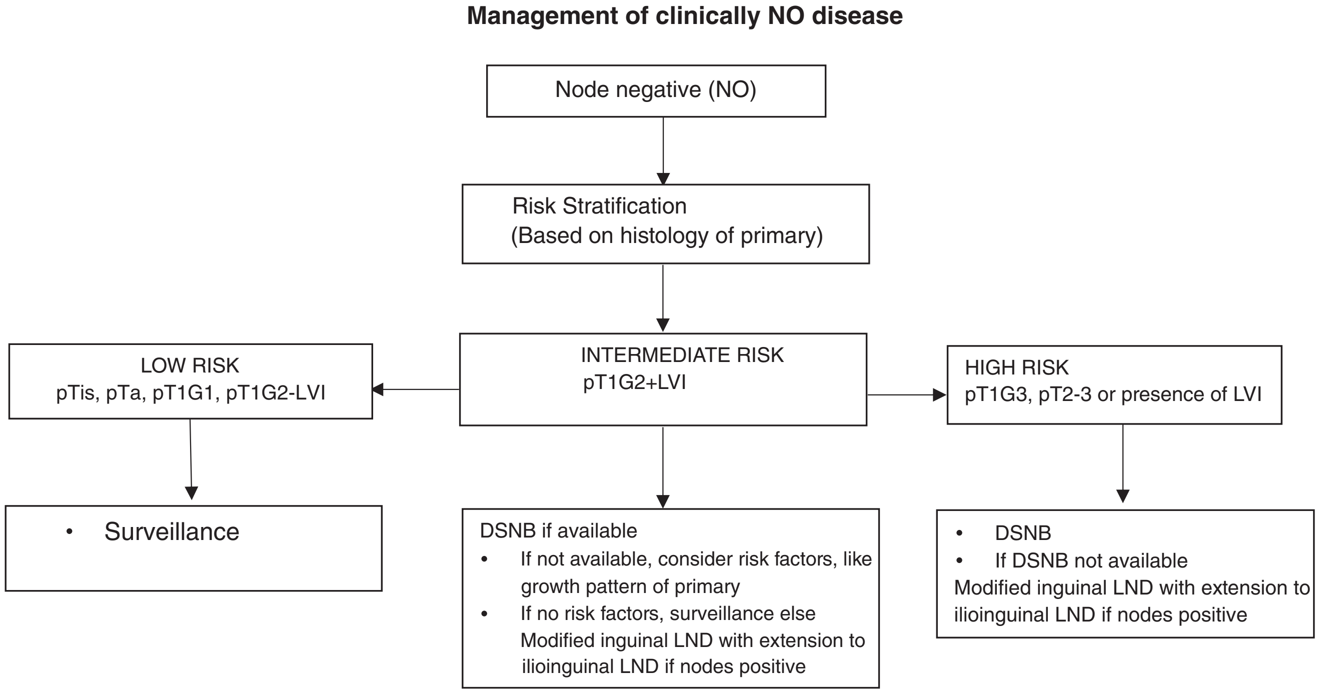
Management of clinically NO disease
Node negative (NO)
Risk Stratification
(Based on histology of primary)
LOW RISK
pTis, pTa, pT1G1, pT1G2-LVI
INTERMEDIATE RISK
pT1G2+LVI
HIGH RISK
pT1G3, pT2-3 or presence of LVI
• Surveillance
DSNB if available
• If not available, consider risk factors, like growth pattern of primary
• If no risk factors, surveillance else Modified inguinal LND with extension to ilioinguinal LND if nodes positive
• DSNB
• If DSNB not available
Modified inguinal LND with extension to ilioinguinal LND if nodes positive

Fig. 7 Treatment algorithm for clinically No disease

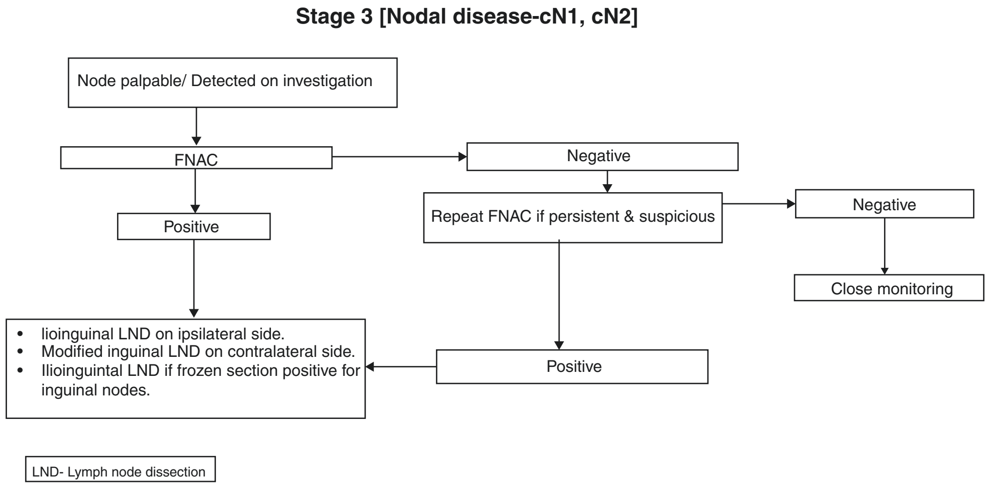
Stage 3 [Nodal disease-cN1, cN2]
Node palpable/ Detected on investigation
FNAC
Negative
Positive
Repeat FNAC if persistent & suspicious
Negative
Close monitoring
• lioinguinal LND on ipsilateral side.
• Modified inguinal LND on contralateral side.
• Ilioinguintal LND if frozen section positive for inguinal nodes.
Positive
LND- Lymph node dissection

Fig. 8 Treatment algorithm for Stage 3 nodal disease

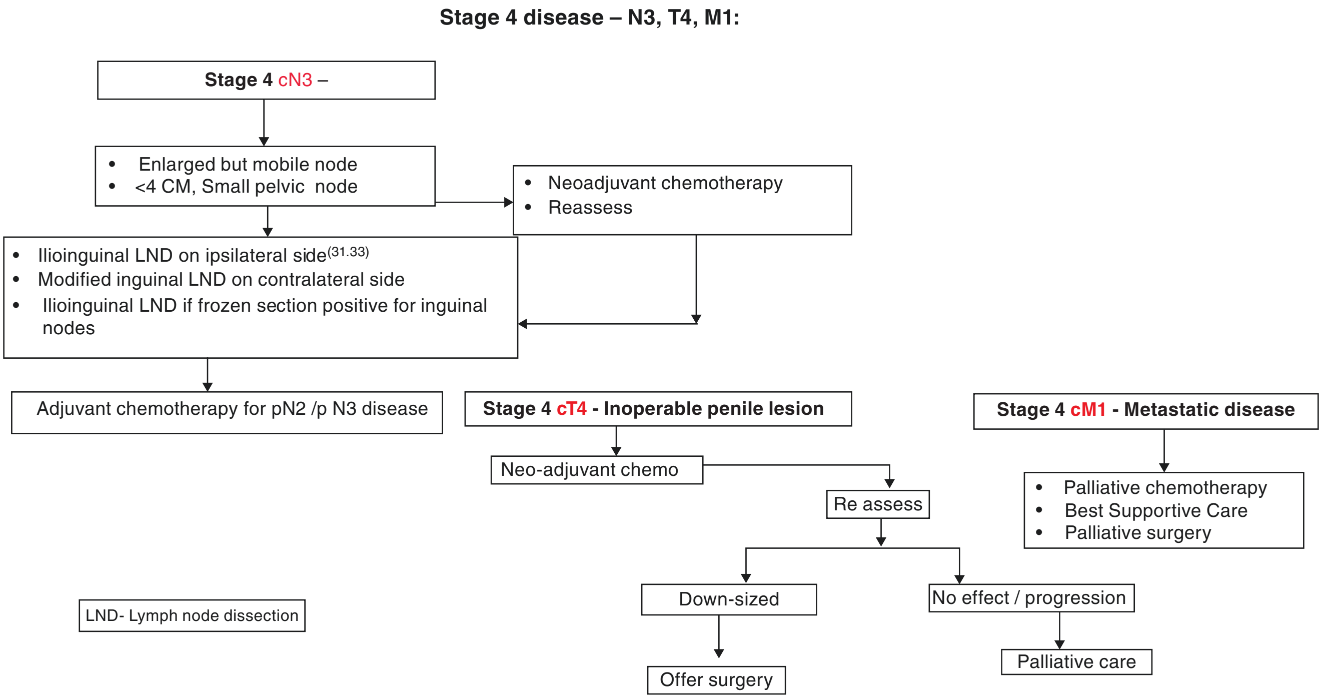
Stage 4 disease – N3, T4, M1:
Stage 4 cN3 –
Enlarged but mobile node
<4 CM, Small pelvic node
Neoadjuvant chemotherapy
Reassess
Ilioinguinal LND on ipsilateral side(31.33)
Modified inguinal LND on contralateral side
Ilioinguinal LND if frozen section positive for inguinal nodes
Adjuvant chemotherapy for pN2 /p N3 disease
Stage 4 cT4 - Inoperable penile lesion
Neo-adjuvant chemo
Re assess
Down-sized
Offer surgery
No effect / progression
Palliative care
Stage 4 cM1 - Metastatic disease
Palliative chemotherapy
Best Supportive Care
Palliative surgery
LND- Lymph node dissection

Fig. 9 Treatment algorithm for Stage 4 disease

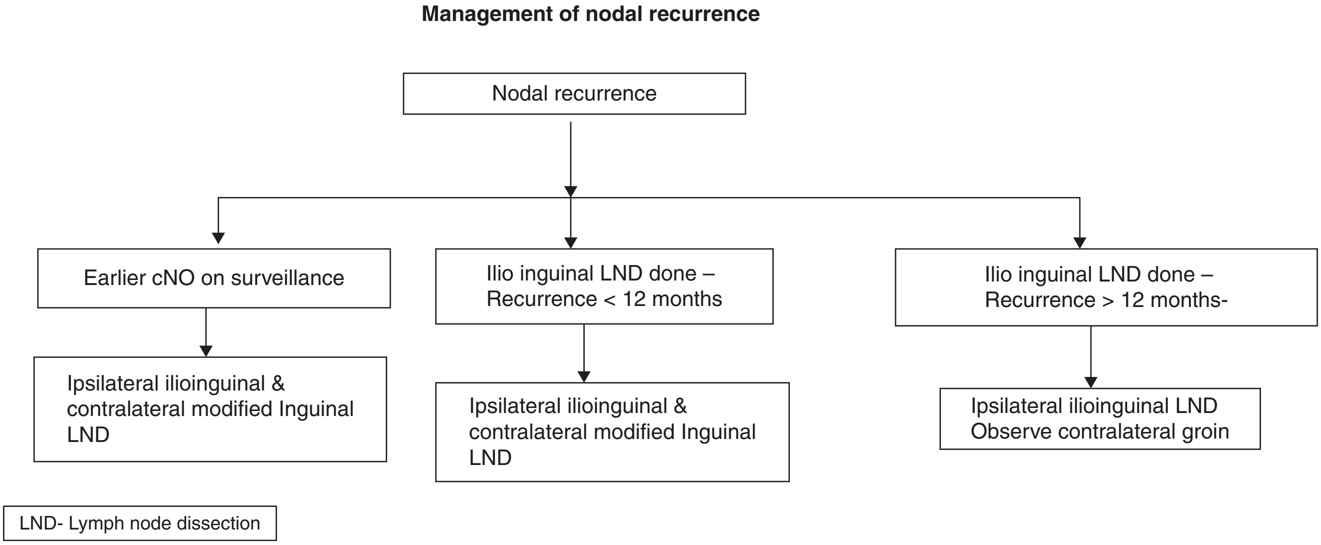
Management of nodal recurrence
Nodal recurrence
Earlier cNO on surveillance
Ilio inguinal LND done – Recurrence < 12 months
Ilio inguinal LND done – Recurrence > 12 months-
Ipsilateral ilioinguinal & contralateral modified Inguinal LND
Ipsilateral ilioinguinal & contralateral modified Inguinal LND
Ipsilateral ilioinguinal LND Observe contralateral groin
LND- Lymph node dissection

Fig. 10 Treatment algorithm for management of nodal recurrence

Nodal recurrences are managed as in Fig. 10. In case of systemic recurrences, follow algorithm of metastatic disease.

11 Stage-Wise Prognosis with Current Rx

As PeCa is uncommon, it is difficult to predict accurate survival rates of the cancer. The figures below regarding survival are from the National Cancer Institute's SEER database, analyzing more than 1000 men diagnosed with penile cancer between 1988 and 2001 [64].

- Stage 1 and 2 disease—5-year survival 85% with surgical management of primary (penile preserving and amputation surgeries). Recurrence rate with penile preserving surgery is 8.9% and with radiation therapy is 15%.
- Stage 3 disease—5-year survival is 59%.
- Stage 4 disease—5-year survival is around 11%.

Table 1 Recommendations for follow-up of the primary tumour

	Follow up interval		Examinations and investigations	Minimum period of follow-up
	Year 1–2	Year 3–5		
Penile-preserving treatment	3 months	6 months	• Physician or self-examination • Repeat biopsy after topical or laser treatment for penile intraepithelial neoplasia	5 years
Amputation	3 months	1 year	• Physician or self-examination	5 years

Table 2 Recommendations for follow-up of the inguinal lymph nodes

	Follow up Interval		Examinations and investigations	Minimum period of follow-up
	Year 1–2	Year 3–5		
Surveillance	3 months	6 months	• Physician or self-examination	5 years
pN0 at initial treatment	3 months	1 year	• Physician or self-examination • Optional: Ultrasound with fine-needle aspiration cytology	5 years
pN+ at initial treatment	3 months	6 months	• Physician or self-examination • Optional: Ultrasound with fine-needle aspiration cytology • Computed tomography/magnetic resonance imaging if indicated	5 years

11.1 Follow-Up

Rationale for follow-up is that early detection of recurrence increases the possibility for patient to undergo curative treatment because local recurrence does not affect long-term survival if successfully treated compared to distant recurrence, which is associated with reduced survival.

Follow-up schedule is based on the type of treatment like penile-preserving surgeries and amputation only or inguinal nodes were also addressed.

Tables 1 presents recommendations for follow-up of the primary tumor, and Table 2 presents recommendation for follow-up of the inguinal lymph nodes.

12 How We Do It at TMC (Table 3)

Table 3 How we do it at TMC

Diagnosis	Local examination	Biopsy of penile lesion (mandatory)	USG (b/l inguinal region and pelvis) In obese patient with low risk disease and for all clinical intermediate and high-risk disease *CT/MRI (abdomen and pelvis)* In selected patient in ≥ N2 disease, previous inguinal or pelvis surgery, obesity *Chest-X ray*	
Treatment	Stage 1 and 2	Penile-preserving approaches, partial or total penectomy	*Address lymph nodes:* Surveillance or prophylactic modified inguinal LND (based on risk stratification).	
	Stage 3	Partial or total penectomy	*Address lymph nodes:* Modified inguinal LND or Ilioinguinal LND	
	Stage 4	Partial or total penectomy Palliative penile surgery	*If operable post NACT*: Ilioinguinal LND *If inoperable post NACT:* Palliative chemotherapy	*In M1 disease,* palliative chemotherapy

LND lymph node dissection, *NACT* neoadjuvant chemotherapy

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Testicular Cancer

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Abbreviations

BEP	Bleomycin, etoposide and cisplatin
CT	Computed tomography
EC	Embryonal carcinoma
GCNIS	Germ cell neoplasia in situ
GCT	Germ cell tumors
GEMOX	Gemcitabine and oxaliplatin
HDCASCT	High-dose chemotherapy and autologous stem cell transplant
IGCCCG	The International Germ Cell Cancer Collaborative Group
LDH	Lactate dehydrogenase
NSGCT	Nonseminomatous germ cell tumor
RPLND	Retroperitoneal lymph node dissection
SMN	Second malignant neoplasms
TNM	Tumor/node/metastasis
USG	Ultrasonography

1 Introduction

Testicular malignancies form a group of rare disorders with an incidence of 1% of all malignancies. Most of all testicular cancers are germ cell tumors (GCTs). The evolution of testicular cancer management is a milestone journey of success in oncology that merits highlighting. The 5-year relative survival is 97% from 2005 to 2011 [1]. However, this also results in many challenges in the management of GCT; the need of the hour is to prevent and mitigate overtreatment and exposure to unwarranted toxicities in patients with good-risk features and ensure an adequate treatment in patients with poor-risk features.

2 Incidence and Epidemiology

Testicular cancer is a very rare malignancy in the Indian context. India's incidence rates for testicular cancer rank among world lowest in the world (0.5 per 100,000 men) [2]. However, the incidence of this disease has been steadily increasing worldwide. In Northern Europe, specifically Norway and Denmark, the incidence of testicular cancers has more than doubled; approximately 1% of men are diagnosed with testicular cancer in their lifetime [3]. In the United States, the incidence has steadily increased over the previous two decades. The incidence of testicular malignancies is the highest among Caucasians and lowest among African Americans [4]. This increase in incidence has fortunately been met with remarkable strides in treatment and outcome, and consequently, the prognosis of testicular cancer is very favorable, mainly in high-income countries.

Risk factors for the development of testicular cancer are family history of testicular cancer (12-fold increased relative risk), cryptorchidism (4–6 time relative risk) and germ cell neoplasia *in situ* (GCNIS).

3 Histological Classification

The histological spectrum of GCTs comprises seminomatous and nonseminomatous (NSGCT) tumors. The types of NSGCT are embryonal carcinoma (EC), yolk sac tumor, teratoma and choriocarcinoma subtypes in pure forms or in various combinations as a mixed GCT, which in turn can also

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contain seminomatous components thus composed of two or more GCT subtypes. For precursor lesions, newer terminology is used, viz., germ cell neoplasia *in situ* (GCNIS).

4 Clinical Presentation

Testicular swelling is often synonymous with testicular malignancies and is seen in approximately 75% of patients. Testicular pain is present in about 8–46% of GGCTs [5]. Acute pain is a feature of torsion or bleeding within the tumor. Other rare manifestations include gynecomastia seen in choriocarcinoma and back pain because of large retroperitoneal lymph nodes and can be detected during the evaluation of infertility.

Testicular masses are usually firm to hard with a normal scrotal sac—the other differential diagnosis of testicular mass is testicular torsion, varicocele, spermatocele and epididymitis.

Varicoceles are described as a "bag of worms" on palpation, and because of engorgement, the venous pampiniform plexus of the spermatic cord. Spermatoceles are found in posterosuperior aspects of the scrotum and trans-illuminate. Testicular cancer is commonly mistaken for epididymitis, marked by swollen and tender testicles. Hence, any patient of epididymitis who fails to respond to a 10-day course of antibiotics should be subjected to a thorough physical examination and evaluation with ultrasonography.

5 Evaluation and Work-Up

5.1 Testicular Ultrasonography

USG of testis differentiates testicular cancer from other entities. The differential diagnoses to be ruled out by USG are testicular torsion, varicocele, spermatocele and epididymitis, with testicular ultrasonography providing high sensitivity and specificity of differentiation and finality of diagnosis. Radiological observation of hypoechoic or heterogeneous lesions should prompt a stringent subsequent evaluation. Negative ultrasonography reliably rules out the presence of intrascrotal GCT [6].

5.2 Orchidectomy

Any patient with a suspected testicular mass clinical examination or testicular ultrasonography should undergo unilateral trans-inguinal orchiectomy with radical intent to rule out testicular carcinoma. Orchiectomy is the gold-standard definitive procedure for both logical diagnosis and local control and maybe a curative approach [7]. Orchidectomy may be delayed when control of metastatic diseases is needed urgently. Despite complete eradication of cancer from the viable metastatic deposits using systemic chemotherapy, orchiectomy is mandatory after completion of systemic chemotherapy to prevent relapse as there are chances of persistence of likely tumor within the testis owing to the presence of the blood-testis barrier [8].

5.3 Tumor Markers

Measuring pre and postorchidectomy levels of HCG, AFP and lactate dehydrogenase (LDH) is essential to stratify the disease exactly. Tumors are the fundamental component of the evaluation of testicular cancer patients and offer diagnostic, staging and prognostic information and help assess disease progression and response to therapy.

HCG is a glycoprotein of 45,000 MW. The half-life of serum hCG is 24 h. HCG consists of alpha and beta subunits. The beta subunit, measured in serum, is produced by the placenta at high levels in adults but low levels in normal nonpregnant adults. Beta hCG is produced by syncytiotrophoblastic cells mainly in choriocarcinomas and seminoma. Very high levels are usually associated with choriocarcinoma. Rarely in seminoma (in 5%–40%), beta hCG elevation can be seen but usually not exceeding 100 mIU/mL [9].

AFP is a protein with a half-life of AFP in serum of 5–7 days [10]. AFP is secreted physiologically in the fetal yolk sac, liver and gastrointestinal tract. The yolk sac component of the germ cell tumor mainly secretes AFP. Rarely embryonal carcinoma and teratoma can also secrets a small quantity of AFP. Patients diagnosed with seminoma and an elevated AFP are assumed to be nonseminomatous components and treated as per NSGCT protocol.

Lactate dehydrogenase (LDH) is another marker that is elevated in testicular tumors and is mainly found in muscle (including smooth, cardiac and striated), liver and brain tissues. Compared to β-hCG, LDH alone is less specific for diagnosing testicular cancer, with LDH-1 being most common and produced by the testis. The half-lives of this isoenzyme vary from 10 hours 3 to days. LDH is commonly used for prognostication of advanced disease in good-, intermediate- and high risk along with B-hCG and AFP [11].

5.4 Radiological Evaluation

Postorchidectomy radiological evaluation is mandatory to detect the spread of diseases in the retroperitoneum and lung. A CT imaging of the chest with the abdomen and pelvis is generally necessary. However, there is a slight controversy over the chest radiography against tomography, although most institutes consider CT scan thorax. It also helps compare the pulmonary nodules in response to therapy and subsequent follow-up.

5.5 Clinical Staging

Serum tumor markers and CT scans are the most used methods for detecting metastatic disease [12] in retroperitoneal adenopathy and lung metastasis. Contrast-enhanced CT scan is the preferred technique for detection. MRI brain is indicated in symptomatic patients and patients with high levels of beta -HCG levels. Similarly, a bone scan is indicated in a symptomatic patient.

5.6 Pathologic Staging

The staging classification of these primary tumors and the lymph nodes and is as follows:

(Table 1) [13] which can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no.732–733, Chapter

Table 1 Staging classification for testicular cancer

Tumor, node, metastases (TNM) staging in testicular cancers	
TNM category	Description
Primary tumor (T)	
pTx	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis	Intratubular germ cell neoplasia
pT1	Tumor limited to the testis and epididymis without vascular or lymphatic invasion. Tumor may invade into tunica albuginea but not tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular invasion or tumor extending through the tunica albuginea with involvement of tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular or lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular or lymphatic invasion
Regional lymph nodes (N)	
Clinical	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass ≥2 cm in greatest dimension or multiple LN, none >2 cm in greatest dimension
N2	Metastasis with a lymph node mass >2 cm but not >5 cm or multiple LN, with any mass >2 cm but none >5 cm
N3	Metastasis with a LN mass >5 cm in greatest dimension
Pathological (pN)	
pNx	Regional LN cannot be assessed
pN0	No regional LN metastasis
pN1	Metastasis with a LN mass ≥2 cm in greatest dimension and ≤5 nodes positive
pN2	Metastasis with a LN mass >2 cm but not >5 cm in greatest dimension, or >5 nodes positive, with none >5 cm; or evidence of extra nodal extension of tumor
pN3	Metastasis with a LN mass >5 cm in greatest dimension
Distant metastases (M)	
M0	No distant metastasis
M1	Distant Metastasis
M1a	Nonregional node or pulmonary metastases
M1b	Distant metastasis other than to nonregional LN and lungs
Serum tumor markers (S)	
Sx	Marker study not available or not performed
S0	Marker study within normal limits
S1	LDH < 1.5 × N and hCG (mIU/mL) <5000 and AFP (ng/mL) <1000
S2	LDH 1.5–10 × N or hCG (mIU/mL) 5000–50,000 or AFP (ng/mL) 1000–10,000
S3	LDH > 10 × N or hCG (mIU/mL) >50,000 or AFP (ng/mL) >10,000

AJCC cancer staging system 2020

N normal limit, *LN* lymph node, *AFP* αfetoprotein, *hCG* human chorionic gonadotropin, *S* serum tumor markers

Table 2 International Germ Cell Cancer Collaborative Group (IGCCCG) risk nonseminoma seminoma

Stage grouping				
Group	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1–4	N0	M0	Sx
IA	pT1	N0	M0	S0
IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
IS	Any pT/Tx	N0	M0	S1–3
Stage II	Any pT/Tx	N0-3	M0	Sx
IIA	Any pT/Tx	N1	M0	S0
		N0	M0	S1
IIB	Any pT/Tx	N2	M0	S0
		N0	M0	S1
IIC	Any pT/Tx	N3	M0	S0
		N3	M0	S1
Stage III	Any pT/Tx	Any N	M1	Sx
IIIA	Any pT/Tx	Any N	M1a	S0
			M1	S1
IIIB	Any pT/Tx	N1–3	M0	S2
		Any N	M1a	S2
IIIC	Any pT/Tx	N1–3	M0	S3
		Any N	M1a	S3
			M1b	Any S

Measured after Orchidectomy. As per AJCC (2020)

no. 59, Testis, Table: Definition of TNM and Definition of Serum Markers (S), which can be accessed at https://emedicine.medscape.com/article/279007-workup#c7

5.7 Prognostic Value and Risk Stratification

Pretreatment (postorchidectomy) tumor marker levels (beta hCG, AFP, LDH) are valuable for staging and prognosis in men with testicular GCTs. Traditional tumor/node/metastasis (TNM) staging is not as proper a predictive tool as in other solid malignancies because the disseminated disease has a greater likelihood of long-term survival.

The International Germ Cell Cancer Collaborative Group (IGCCCG) now recommends serum tumor markers as a prognostic indicator in GCTs. In the IGCCCG schema, pretreatment (postorchidectomy) levels of serum beta hCG, AFP and LDH are independent predictors of risk, along with the site of primary disease and the presence of nonpulmonary visceral metastases [14]. The IGCCCG risk stratification system is described separately (Table 2).

6 Management of Clinical Stage I Disease

Almost every patient with clinical stage I germ cell tumors will survive. Stage I germ cell tumors have a cancer-specific survival of 98% to 99% [15]. Further, patients who have received adjuvant intervention have the same life expectancy as on observation. Hence, cost, the burden of the therapy and patient preference are the key guiding factors for treatment decisions.

Seminoma: Stage I seminoma is a joint presentation accounting for 70% of the disease burden. Risk stratification of Clinical stage I seminoma into high-risk and average risk is based on tumor size. Still, similar options exist for all patients with stage I seminoma, regardless of risk [15, 16]. Generally, they are diagnosed on the postorchiectomy specimen. The diagnosis of stage I seminoma is based on the following findings: histologic diagnosis of pure seminoma (without any evidence of nonseminomatous elements) on final pathologic analysis of the orchiectomy specimen. No pretreatment elevation of alpha-fetoprotein and no evidence of lymph node involvement or distant metastases based on staging computed tomography (CT) of the thorax, abdomen and pelvis (radiographer CT). Regular tumor marker studies following orchiectomy.

Eighty-five percent of the patients with stage I seminoma are cured by orchiectomy alone.

About 20% of the patient's risk of recurrence without any adjuvant therapy. Many retrospective studies have defined the risk of recurrence in these patients, i.e., tumor size more than 4 cm and invasion of rete testes [17, 18]. The treatment options for these patients include the following [17–19]:

- Orchiectomy followed by active surveillance.
- Orchiectomy followed by single-agent carboplatin.
- Orchiectomy followed by radiation therapy.

6.1 Surveillance

Approximately 15–20% of stage I seminoma will relapse if no further treatment is offered. The probability of recurrence in high-risk tumors more than 4 cm or with rete testis involvement is 30% to 35%, whereas patients with tumors less than 4 cm without rete testis involvement have a risk of only 12% [20]. Recurrences are temporally distributed over 10 years [21]. Retrospective series from the Royal Marsden Hospital London, from the Princess Margaret Hospital (PMH), Toronto, and from national collaboration in Denmark, have all concluded that surveillance is a reasonable policy [20].

Surveillance is a feasible option as these patients, if they recur, can have a similar cure rate by the salvage regimen compared to patients who receive radiation therapy or chemotherapy in an adjuvant setting. These patients, however, require periodic CT scanning as tumor markers are not elevated in Seminoma, and these patients usually recur in retroperitoneum.

Active surveillance is practiced to prevent the second malignancy as these patients are long-term survivors, and all do not require adjuvant therapy. Those patients who do recur can be salvaged safely.

6.2 Adjuvant Chemotherapy

Cisplatin-based combination chemotherapy is the backbone for treating advanced-stage testicular germ cell tumors. Carboplatin is often preferred in stage I seminoma because of its better toxicity profile. Carboplatin has better safety and toxicity profile than radiotherapy for stage one disease. In a noninferiority trial of carboplatin with radiotherapy enrolled 31,477 patients. They compared adjuvant para-aortic RT (para-aortic strip or dog-leg field and 20 or 30 Gy depending on the center) versus a single-cycle carboplatin CHT (area under the curve [AUC] of 7 mg/mL/min) [22]. This noninferiority trial established a comparable 3-year disease-free survival time between both arms (94.8 vs. 95.9%; $p = 0.32$) [23]. Both RT and carboplatin were well tolerated with different toxicity profiles. There were more frequent retroperitoneal recurrences after adjuvant carboplatin, so follow-up CT scans are mandatory. There were no reported instances of second malignant neoplasms (SMN) in patients treated with chemotherapy, and fewer contralateral germ cell tumors were reported compared to radiotherapy at medium-term follow-up.

The Current recommendation with carboplatin is to administer a single carboplatin dose that is appropriately dosed by renal scintigraphy for two cycles at three weekly intervals. There are no randomized trials of two cycles of carboplatin versus one process. Several phase II trials have shown benefits in reducing recurrences with two cycles of carboplatin; however, longer follow-up and a phase III study are needed to establish this approach.

Adjuvant Radiotherapy: A dose of 20 Gy to the para-aortic lymph nodes helps achieve excellent local control of nearly 100%. In the MRC trial, comparing 30 Gy with 20 Gy establishes equivalence in recurrence in both the arms [24]. Less toxicity in terms of infertility and other gastrointestinal effects is associated with the sparing of ipsilateral lymph nodes from the treatment field. For clinical stage I seminoma, the recurrence rate is as low as 4% after prophylactic radiotherapy, and the survival rates are significantly high with combination chemotherapy. Out of field recurrence in pelvic nodes and lungs can be seen occasionally. The contraindications for radiotherapy are patients with horseshoe kidney or inflammatory bowel disease. The ipsilateral scrotal contents and inguinal orchiectomy scar should be treated if a scrotal violation has occurred during surgery. After MRC publication, the 20 Gy dose option with a 2-week treatment time is the standard practice. Using this approach, the disease-free survival is close to 95%, and the long-term disease-specific survival rate is approximately 100% [25]. However, this approach is associated with an increased risk of second malignancies such as gastrointestinal and genitourinary [26]. With time, the use of prophylactic RT for stage I seminoma is declining gradually, and single-agent carboplatin is the preferred choice.

6.3 Pure Seminoma Stages IIA and IIB

Stage IIA and IIB pure seminoma comprise metastatic disease to lymph nodes measuring ≤2 cm (II A) and between 2 and 5 cm in size (II B). Patients with stage IIA and stage IIB seminomas can be treated with either RT or chemotherapy with three cycles of bleomycin, etoposide and cisplatin (BEP) or four cycles of etoposide and cisplatin (EP) [27]. Glaser et al., in a retrospective study, compared RT with multiagent chemotherapy in stage IIA–C seminoma patients. They concluded that 15-year OS was statistically higher in RT arm compared to chemotherapy arm, mainly in stage IIA patients (99% vs. 93%; HR, 0.28; 95% CI, 0.09–0.86; $P = 0.027$) [28]. Hence, the recommended treatment for Stage IIA disease is RT, while chemotherapy is the preferred therapy for Stage II B.

6.3.1 Follow-up for Pure Seminoma Stages IIA and Nonbulky IIB

After Primary Treatment

For stage IIA and nonbulky location IIB seminoma, the recommended follow-up schedule includes physical examination, history and serum tumor markers (AFP, beta HCG, LDH) post orchiectomy, which should be performed every 3 months during the first year and every 6 months from second to the fifth year. A chest x-ray is recommended every 6 months for the first 2 years. An abdominal CT scan with or without a pelvic CT scan is recommended for 3 months, 6 months and 12 months in the first year and then annually from the second to the fifth year. Unless clinically indicated beyond 5 years CT is not recommended.

6.4 Pure Seminoma Stages IIC and III

6.4.1 Primary Treatment for Pure Seminoma Stages IIC and III

Patients with stage IIC or stage III seminomas are classified as either excellent or intermediate risk based on the site of metastasis.

All stage IIC and stage III seminomas are considered good-risk diseases, except those with nonpulmonary visceral metastases (e.g., bone, liver, brain), which are regarded as an intermediate-risk diseases. The recommended treatment for patients with good-risk disease is three cycles of BEP or four cycles of EP [29, 30]. For patients with intermediate-risk disease, the recommended treatment is with four cycles of BEP or four cycles of etoposide, mesna, ifosfamide and cisplatin (VIP) [22, 31].

6.4.2 Immediate Follow-Up of Pure Seminoma Stages IIA, IIB, IIC and III

CT scan with contrast of chest, abdomen and pelvis with serum tumor markers (AFP, beta HCG) is recommended for patients with stages IIA, IIB, IIC and III seminoma after chemotherapy. Patients are then classified according to the presence and absence of residual disease in CT Scan. For patients with residual disease of more than 3 cm in CT scan, another investigation that has been recommended for evaluation of seminoma of patients is PET-CT, which should be done after 8 to 10 weeks of completion of chemotherapy [32, 33]. Surveillance is recommended if the PET scan is negative. If the PET scan is positive, the lesion must be resected/biopsied and subjected to histopathology examination. If the complete resection is done and HPE shows viable Seminoma then consider two cycles of EP or two cycles of other second-line regimen TIP (paclitaxel, ifosfamide, cisplatin), VIP or VIP (vinblastine, mesna, ifosfamide, cisplatin).

If the resection is incomplete and viable seminoma is present on HPE, then consider the course of second-line chemotherapy (4 cycles of TIP or four cycles of VIP or VeIP) [34]. If biopsy results are negative for viable seminoma, surveillance is recommended [35].

6.4.3 Follow-Up for Pure Seminoma Bulky Stage II and Stage III After Chemotherapy

Recommended follow-up schedule for patients with bulky stage II/stage III seminoma treated with chemotherapy consists of two monthly clinical examination and serum tumor marker assessment for the first year, the frequency of visit could be reduced to every 3 months in second year and further decreased to 6 months in third and fourth years and once in the fifth year. Beyond 5 years, CT imaging is recommended only when clinically indicated.

The patients also need to undergo thoracic imaging with an X-ray chest at a frequency of 2 monthly in the first year, 3 months in the second year and yearly through the third to fifth years.

6.5 Nonseminomatous Germ Cell Tumor

Management of clinical stage I NSGCT is divided and stratified as high risk and average risk. LVI has been validated as a risk factor because there are differences in the presentation of tumors including size, histology and tumor marker. NSGCT with LVI has been almost 50% of recurrence rate with observation. Within 2 to 3 years of orchiectomy, most relapses are expected. In "good-risk" stage I, the overall possible risk of relapse is approximately 30%, with patients with LVI-negative NSGCT having a chance of recurrence <30%. The risk of recurrence of stage I NSGCT with LVI negative with mainly embryonal carcinoma histology is higher than other NSGCT at 30% to 50%.

6.6 Surveillance

Retroperitoneal lymph nodes are a common site for relapse in patients on surveillance in approximately two-thirds of cases. Thee in the standards of one tone-third only show marker elevation alone without evidence of any focal site of relapse. Recurrences in nonpulmonary viscera are rare. Within 2–3 years of postorchidectomy, relapses occur; patients need follow-up for at least 5 years. Even those relapses, cisplatin-based chemotherapy has shown good results. Surveillance is not recommended for those who are anticipated to be poorly compliant. Observation is considered in most cases with the LVI-negative, clinical stage I NSGCT. There are no clear consensus on managing patients with pT2-pT4 tumors (including LVI-positive). Adjuvant chemotherapy I preferred treatment for LVI-positive or advanced T classification NSGCT; however, in patients with nonbulky (<5 cm) retroperitoneal disease and normal serum AFP and hCG levels and with the availability of experienced surgeon, RPLND can also be considered [34, 36].

6.7 RPLND

Retroperitoneum being the most common site for occult metastasis is targeted for disease control in the form of RPLND in patients with clinical stage I NSGCT without evidence of systemic disease. High cure rates have been observed in patients undergoing RPLND for occult retroperitoneal metastasis and teratoma. The lowest risk of abdominopelvic recurrence is observed when a complete bilateral template dissection is performed and high rates of antegrade ejaculation (>90%) are expected when nerve-sparing techniques are used. The least benefitted patients from RPLND are with stage IA embryonal carcinoma-predominant tumors, probably because of the tendency to spread via hematogenous route and thereby increase the risk of recurrence in lungs.

6.8 Adjuvant Chemotherapy

Bleomycin, etoposide and cisplatin (BEP) form backbone of primary chemotherapy. Several published studies are using either a single course or a double course of adjuvant BEP or clinically acceptable analogous regimens in patients with clinical stage I NSGCT [37]. The continuing risk of growing teratoma syndrome is an unwanted accompaniment to adjuvant chemotherapy and presents a limitation in adjuvant management. RPLND can only remove teratoma syndrome. By shortening treatment to one course BEP based over two, the toxicity of adjuvant chemotherapy is reduced.

This is based on encouraging results from various European trials, which showed recurrence rate of less than 5% with a single cycle of BEP with very few and acceptable toxicities and decreased rate of developing growing teratoma syndrome.

6.9 Stage IS

In Stage IS, serum tumor markers remain persistently elevated after radical orchiectomy with the absence metastatic disease and radiographic evidence of disease. Other causes of elevated levels of AFP and beta-HCG must be considered including hepatobiliary disease, marijuana use or hypogonadism. Clinically looking at pattern of tumor markers, may provide some clue regarding its etiology. Progressively rising markers may point to the malignant cause while stable markers point to the other cause than the malignancy. Elevated markers are generally in S1 markers range. Considering a disseminated disease in the absence of radiological site, the treatment is three courses of BEP or four courses of EP.

Management of Clinical Stage II: Metastasis limited to retroperitoneal lymph nodes is classified as Stage II GCT with S0 to S1 tumor markers. Most of these patients are cured with standard treatment as outlined below.

6.10 Clinical Stage IIA

Postorchiectomy serum AFP and beta-HCG levels are used as a cornerstone for guiding the response and treatment in patients with stage IIA NSGCT. Patients with normal postorchiectomy levels of AFP and beta-hCG can be treated with either chemotherapy with three cycles of BEP or four cycles of EP as primary treatment options or with nerve-sparing RPLND [38, 39]. Generally, for multifocal disease, chemotherapy is considered appropriate.

Management of nonseminoma Stage IIA: After Primary Treatment on the number of positive lymph nodes, treatment options following primary nerve-sparing RPLND are based. Patients with pN0 disease post-RPLND is surveillance. For the pN1 disease, the preferred choice is surveillance; however, chemotherapy with two cycles of BEP/ EP can be given. The recommended treatment for pN2 disease is two cycles of adjuvant chemotherapy with EP or BEP and full course of chemotherapy for pN3 disease (either three cycles of BEP or four cycles of EP) [40].

Tumor marker levels and the size of residual mass on CT scan dictate management after primary chemotherapy. CT abdominal/pelvic CT scans/chest CT with contrast is performed after completing chemotherapy to look for residual adenopathy. The nerve-sparing RPLND is recommended for patients with a residual mass ≥1 cm. For patents with normal tumor markers residual mass <1 cm surveillance is recommended.

6.11 Nonseminoma Stage IIB

Primary Treatment for Nonseminoma Stage IIB: Treatment for patients with stage IIB nonseminoma depends on postorchiectomy serological and radiological response. When postorchiectomy tumor marker levels respect normal ranges, the CT findings determine the proper course of treatment. If abnormal radiographic findings are limited to the lymphatic drainage sites within the retroperitoneum (i.e., the landing zone), primary chemotherapy with either three cycles of BEP or four cycles of EP must be given. RPLND as primary treatment must be reserved for highly selected cases. The outcomes are similar with both approaches but differ with respect to side effect profile. The documented relapse-free survival is 98% with either approach [41]. Either four cycles of EP or three cycles of BEP are recommended as first-line chemotherapy if metastatic disease (based on radiographic findings) lies outside the lymphatic drainage sites (i.e., multifocal lymph node metastases with aberrant lymphatic drainage sites. The recommended treatment for stage IIB nonseminoma patients with persistent marker elevation is primary chemotherapy with either three cycles of BEP or four cycles of EP.

6.12 Advanced Metastatic Nonseminoma

The management of the advanced metastatic nonseminoma are based on whether the tumor is good, intermediate or poor risk by IGCCCG risk classification [14]. The risk is determined based on primary site of the germ cell tumor, stage of the disease and the tumor markers done on cycle 1 day one of first-line chemotherapy [42].

6.13 Primary Treatment for Good-Risk Nonseminoma

Stages IS, IIA, IIB, IIC and IIIA diseases include in IGCCCG good-risk group. Treatment for good-risk GCT consist of either four cycles of EP or three cycles of BEP. By above regimen approximately 90% of patients are cured with good-risk disease [43].

6.14 Primary Treatment for Intermediate-Risk (Stage IIIB) Nonseminoma

The standard treatment for these patients is four cycles of BEP or four cycles of VIP who may not be a candidate for Bleomycin therapy [22, 44]. The cure rate for these patients is approximately 70% with the standard chemotherapy regimen of four cycles of BEP [45].

6.15 Primary Treatment for Poor-Risk (Stage IIIC) Nonseminoma

For poor-risk patients the standard chemotherapy regimen is four cycles of BEP or alternatively four cycles of VIP [46]. In these poor-risk patient, 20% and 30% of patients are not cured with conventional cisplatin-based chemotherapy and <50% experience a long-standing, durable, complete response to four cycles of BEP.

6.16 Management of Good-, Intermediate- and Poor-Risk Nonseminoma

CT scans with contrast of chest, abdomen and pelvis with measurement of tumor markers are indicated to assess treatment response after conclusion of primary chemotherapy. If the CT is suggestive of absence of any disease and tumor markers are normal the recommendation is to put the patient on surveillance. Surgical resection of masses is recommended, if CT scan means PR and the tumor markers are normalized. It is usually recommended to perform RPLND within 7 to 10 days of tumor marker measurement and within 4 weeks of CT scan. Post-RPLND/resection of the residual mass's histopathology is reviewed. If the histopathology examination shows only necrotic debris or mature teratoma surveillance is advised. If histopathology shows embryonal, yolk sac, choriocarcinoma or seminoma elements two cycles of chemotherapy (EP, VeIP, VIP or TIP) is given. Patients with persistently elevated AFP and beta-hCG levels and with an incomplete response to chemotherapy are treated with either close surveillance or surgical resection of residual masses.

6.17 Central Nervous System Metastases

CNS metastasis can occur in patients with germ cell tumor. However, unlike other malignancies, few patients with brain metastasis are also curable [47]. In case of asymptomatic brain metastasis can be initially managed by chemotherapy with good response to therapy. Craniotomy is required in those with active bleeding. Postchemotherapy cycles residual lesion can be treated with radiotherapy, i.e., either SBRT or whole brain radiotherapy. Sometimes, shortly after completion of chemotherapy, patients may present with brain as solitary site of recurrence. These patients can be treated with curative intent with surgery.

6.18 Choriocarcinoma Syndrome

Metastatic choriocarcinoma is characterized by the following key elements-

1. Very high serum hCG levels usually more than one lakh
2. Either as testicular mass or mediastinal primary
3. Can have extensive lung metastasis
4. Other nonpulmonary visceral sites (liver, brain)
5. Tumor hemorrhage via hemoptysis, hemoperitoneum or intracranial bleed)
6. Hyperthyroidism [48].

Patients with choriocarcinoma syndrome are at a risk of complication like hemorrhage and recurrent/refractory disease and can have high rate of complications and death. Early diagnosis and early instillation of treatment decreases the above said complication. Generally patient with high beta HCG levels are at the risk of hemorrhage specially in those with pulmonary metastasis, are treated with EP chemotherapy for 3 days in the first cycle to reduce the risk of complication. For the subsequent cycles 2BEP or an ifosfamide containing regimen is given. Chemotherapy can be started as soon as the diagnosis is made and orchidectomy should be performed between cycles when the patient has stabilized, or at the time of RPLND.

Mediastinal Nonseminomatous Germ Cell Tumor: The most common presentation in this extragonadal NSGCT is in the anterior mediastinum of an adult man. Mediastinal GCT risk is increased in patients with Klinefelter syndrome [49]. One of the proposed theories, for the causation of extragonadal NSGCT is the arrest of migration of germ cells along the urogenital ridge during embryogenesis. The cure rate of mediastinal GCT is lower than most testicular germ cell tumors. The estimated 3-year progression-free survival is being in the range of 48–54% [50].

The primary chemotherapy is four cycles of BEP with good lung function and four cycles of VIP in patients who can't tolerate bleomycin.

Mediastinal primary tumors have a high incidence of viable germ cell malignancy, teratoma and transformation to somatic malignancy in postchemotherapy resections, so surgical consolidation is essential.

7 Management of Recurrent Disease

Second-line Therapy: After receiving the first-line therapy those with recurrence or those who fail to have complete response to first-line therapy are eligible for the second-line therapy or salvage therapy. These patients divided into favorable or unfavorable prognostic groups based on prognostic factors [51]. Low levels of postorchiectomy AFP and beta-HCG, low-volume disease, complete response to first-line therapy and the presence of a testicular primary tumor constitute favorable prognostic factors. Unfavorable prognostic features comprise an incomplete response to first-line therapy, high levels of tumor markers, high-volume disease and the presence of an extratesticular primary tumor. The favorable or unfavorable prognostic factors decides the management in second-line setting which include chemotherapy which is divided into conventional-dose and high-dose chemotherapy. Chemotherapy regimen includes either TIP or VeIP as conventional-dose regimen and high-dose carboplatin plus etoposide or paclitaxel plus ifosfamide forms high-dose regimen followed by autologous stem cell transplant [52]. Patients with unfavorable prognostic factors are usually considered for high-dose regimens. For those with solitary site of disease like single CNS metastasis, surgical resection can be considered. Successful salvage is possible in 50% of cases in first recurrence after BEP chemotherapy. The relapse-free survival with high-dose chemotherapy and autologous stem cell transplant (HDCASCT) in one retrospective study was 60% and is an alternate attractive option. Late relapses (>2 years after completion of primary therapy) occur in 2–3% of testicular cancer survivors.

7.1 Post-Second-Line Therapy

As after the first-line therapy, those receiving second-line therapy must undergo contrast enhanced radiological response assessment of the chest, abdomen, pelvis via Computed Tomography and serological assessment by measurement of serum tumor markers. Those patients with complete radiological response and normal tumor markers can be placed on surveillance.

Surgical resection of all residual masses is recommended for those patients with a partial response to second-line therapy and normal marker levels, while those with an incomplete response and persistently elevated marker levels should be subjected to surgical resection of residual masses, if possible, followed by surveillance.

7.2 Palliative Therapy

The palliative chemotherapy options include combinations of gemcitabine with paclitaxel and/or oxaliplatin [53, 54]. Further, all patients with intensively pretreated, cisplatin-resistant or refractory disease should be considered for palliative therapy. Based on Phase II trials where we investigate efficacy and toxicity, gemcitabine and oxaliplatin are recommended in patients with refractory cisplatin. The recommendation for gemcitabine and oxaliplatin (GEMOX) is based on phase II studies investigating the efficacy and toxicity of GEMOX in patients with relapsed or cisplatin refractory GCTs which safety and efficacy in these group of patients [55]. Based on the various phase II trials for patients with unresectable disease or metastatic MSI-H or mismatched repair deficit (dMMR), PD1 antibody pembrolizumab has been recently approved by the FDA for patients. Pembrolizumab, a PD-1 antibody, has been recently approved by the FDA in patients with unresectable or metastatic MSI-H or mismatch repair-deficient (dMMR) solid tumors that have progressed following prior treatment and for those patients in which there are no other satisfactory alternative treatment options.

In the first phase II trial, Pembrolizumab showed activity in patients with nonseminoma GCTs who progressed after first-line cisplatin-based chemotherapy and at least one salvage regimen (high-dose or conventional-dose chemotherapy) [56]. The maximum response achieved was SD, and it was well tolerated. So larger phase III trials are required in metastatic refractory testicular cancers and are needed to fully assess the value of this therapy, especially in those with MSI-H/dMMR GCTs.

7.3 Retroperitoneal Lymph Node Dissection (RPLND)

RPLND provides critical staging information and is always to be performed with a curative intent. Either transabdominal or thoracoabdominal approaches are available for surgical exposure for RPLND Surgical Exposure for RPLND is achieved through either a transabdominal or thoracoabdominal approach. Supra hilar dissection has been replaced by RPLND template, this has proven to be a game-changer and has replaced the supra hilar dissection. It is now the standard against which therapeutic alternatives are judged. Template for bilateral standard infrahilar RPLND consist of bilateral ureter (laterally), renal hilum (superiorly), bifurcation of iliac vessels (distally). A bilateral infra hilar RPLND includes the precaval, retrocaval, paracaval, inter aortocaval, retroaortic, preaortic, para-aortic and common iliac lymph nodes bilaterally. To minimize the possibility of a late paracolic recurrence, the ipsilateral gonadal vessel must be completely excised. Template for modified right RPLND consist of ureter (laterally), midpoint of aorta (medially), bifurcation of iliac vessels (inferiorly). and renal hilum (superiorly). Template for modified left RPLND consist of ureter (laterally), midpoint of vena cava (medially), bifurcation of iliac vessels (distally) and renal hilum (superiorly). 5 Chances of successful ejaculation are maximized by Modified RPLND templates by limiting dissection in areas thought to be at reduced risk of metastatic spread based on surgical mapping studies. This approach minimizes contralateral dissection, thereby reducing trauma to the hypogastric plexus and contralateral postganglionic sympathetic fibers. In the primary or postchemotherapy setting, nerve-sparing techniques can be used. In a nerve-sparing RPLND, both sympathetic chains, the postganglionic sympathetic fibers and hypogastric plexus are prospectively identified, dissected and preserved. Antegrade ejaculation is preserved in over 95% of all patients with prospective nerve-sparing techniques, that is why actual value of templates to prevent ejaculatory function loss is reduced. Whatever the approach chosen by the surgeon, the preservation of the margins of resection remains the primary priority and must not be compromised to preserve ejaculation.

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Uterine Cancer

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Abbreviations

AH	Atypical hyperplasia
ASR	Age standardized rate
ASTEC	A study of endometrial cancer
CSS	Cancer-specific survival
CT	Computed tomography
DW	Diffusion weighted
EBRT	External beam radiation therapy
EC	Endometrial cancer
EEC	Endometroid endometrial carcinoma
EIN	Endometrial intraepithelial neoplasia
GRH	Gonadotropin-releasing hormone
HNPCC	Hereditary nonpolyposis colon cancer
LVSI	Lymphovascular space invasion
MPA	Medroxyprogesterone acetate
MRI	Magnetic resonance imaging
OS	Overall survival
PET	Positron emission tomography
SEPAL	Survival effect of para-aortic lymphadenectomy
USPIO	Ultrasmall superparamagnetic iron oxide
VBT	Vaginal brachytherapy

1 Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in the developed world and the second most common gynecological malignancy after cervical cancer in the developing world [1]. Majority of the patients (about 75%) present early with the disease being limited to the uterus and the cervix and about 68% percent of women at diagnosis have localized disease [2]. Surgical management forms the primary modality of treatment and adjuvant treatment in the form of radiotherapy or/and chemotherapy is required depending upon stage and risk factors.

2 Incidence

Endometrial cancer comprises 4.4% of all malignancies in females and ranks sixth in the order of cancers afflicting females. GLOBOCAN 2018 estimates 282,069 new cases of EC across the world accounting for 2.1% of all new cancer cases with an estimated mortality accounting for 0.9% of cancer-related deaths worldwide [1]. There is a varied incidence pattern across socioeconomic regions with an age standardized rate (ASR) of 11.1/100,000 women in High development index regions and ASR of 3.3/100,000 women in low/medium development index regions. Incidence in India is reported to be lower. As per the ICMR PBCR data, there is a significant geographical variation in the incidence of endometrial cancer across India also with Chennai topping the list with an ASR of 6/100,000 women and Manipur being the lowest with an ASR of 0.3/100,000 women [3].

3 Epidemiology

EC is a disease of the perimenopausal and post-menopausal age group and more than 90% cases occur in women older than 50 years of age. Median age at diagnosis is 63 years; however, EC occurs almost a decade earlier in Indian women

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with median age at diagnosis of 54 years. Less than 5% of all cases may occur in young women aged less than 40 [4].

Endometrial cancers have traditionally been classified into two main clinicopathological and molecular types. Type I comprising endometrioid adenocarcinoma (80–90%) and Type II formed by the non-endometrioid histologies [5]. Type I EC are associated with genetic alteration in PTEN, KRAS, PIK3CA, MLH1 promoter hypermethylation, whereas type II are associated with TP53 mutations [6]. The Cancer Genome Atlas (TCGA) has now established four molecular subtypes: (1) POLE (ultramutated) tumors, (2) microsatellite unstable tumors, (3) copy number high tumors with mostly TP53 mutations, and (4) remaining group without these alterations [7].

4 Risk Factors

Type I endometrial cancers are commonly associated with prolonged estrogen exposure. Some of the factors responsible include estrogen replacement therapy, metabolic syndrome, chronic anovulation (polycystic ovarian disease), estrogen-producing tumors (granulosa/theca cell tumors of ovary), peripheral conversion of androgens to estrone in adipose tissue, and tamoxifen use. Women who are nulliparous, infertile or those who have early menarche or late menopause are also at an increased lifetime risk of developing EC. Metabolic syndrome has a relative risk of 1.89 for the causation of endometrial cancer with the strongest association being with obesity (RR-2.21).

Certain genetic disorders are also associated with a high risk for developing EC. Lynch syndrome or hereditary nonpolyposis colon cancer (HNPCC) is inherited in an autosomal dominant fashion which results in an increased risk of developing malignancies due to a defect in DNA mismatch repair. The risk of developing EC by 70 years of age is highest for a mutation in MLH1 (54%) followed by MSH2 (21%) and MSH6 (16%). Women with Lynch syndrome develop EC at a much younger age compared to the general population with median age at diagnosis being 46 years [8]. Women with Cowden syndrome (germline PTEN mutation) are at an increased risk for breast, thyroid, and endometrial cancers.

5 Clinical Presentation

EC classically present as abnormal uterine bleeding. EC is the cause of 15% of all cases of postmenopausal bleeding. EC should be excluded in all postmenopausal women with pyometra, perimenopausal women with menorrhagic cycles or intermenstrual bleeding, symptomatic premenopausal women with a prior history of PCOS, symptomatic post-menopausal women on tamoxifen or asymptomatic postmenopausal women with atypical glandular cells in pap smear. EC can also present as abnormal vaginal discharge or incidentally detected thickened endometrium in ultrasound examination performed for a different indication. In advanced stages with peritoneal disease, EC may present similar to advanced ovarian cancer like abdominal pain and distension.

6 Evaluation and Work-up

Basic evaluation starts with general physical examination including a detailed pelvic and abdomen examination. Women with a history of postmenopausal bleeding are usually evaluated initially with a transabdominal and a transvaginal ultrasound (TVS) which reveals endometrial thickening. The USG cut off for endometrial thickening is considered to be 5 mm. Data reviewed from 13 published studies accounting for nearly 2900 patients showed that the 5 mm cut off resulted in a high sensitivity and specificity of 90% and 54% respectively. If the cut off is lowered to 3 mm it offers only a slight increase in sensitivity (98%) while at the same time significantly compromising specificity (35%) [9].

Delineation of tumor margins on TVS can be difficult, especially when it is diffusely infiltrating the myometrium. The use of saline infusion (i.e., sonohysterography) increases the accuracy of TVS to 84–89% in evaluating deep myometrial invasion. There are reports though suggesting an increase in pelvic dissemination of disease on using saline infusion hysterography.

EC appears as a hypoattenuating and hypoenhancing mass in the endometrial cavity on contrast-enhanced computed tomography (CECT). However, this appearance is nonspecific, and the differential diagnosis includes submucosal leiomyomas, endometrial polyps, or cervical stenosis. CECT has a poor sensitivity and specificity for determining myometrial invasion ranging from 40 to 75% and is thus currently used mainly for evaluation of nodal involvement and metastatic disease [10] (Fig. 1).

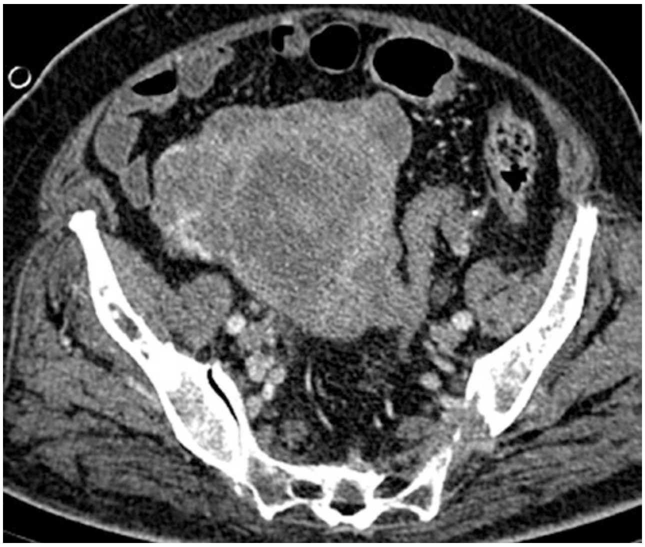

Fig. 1 CECT scan (axial section) uterine surface involved (Stage IIIA)

Magnetic resonance imaging (MRI), owing to its high spatial resolution, is the imaging modality of choice for local staging of EC with overall staging accuracy between 83 and 92%. On MRI, EC is usually seen as a hypo-to-isointense mass on T1-weighted images (T1WI) with an intermediate signal intensity on T2-weighted images (T2WI). On dynamic post-contrast images, EC is hypo enhancing. The sensitivity and specificity of MRI for identification of deep myometrial invasion are around 80% each, with a positive predictive value (PPV) of 86% [11] (Fig. 2). Functional MRI constitutes a profusion of sequences that allow for comprehensive biological assessment of a tumor and is emerging as a useful

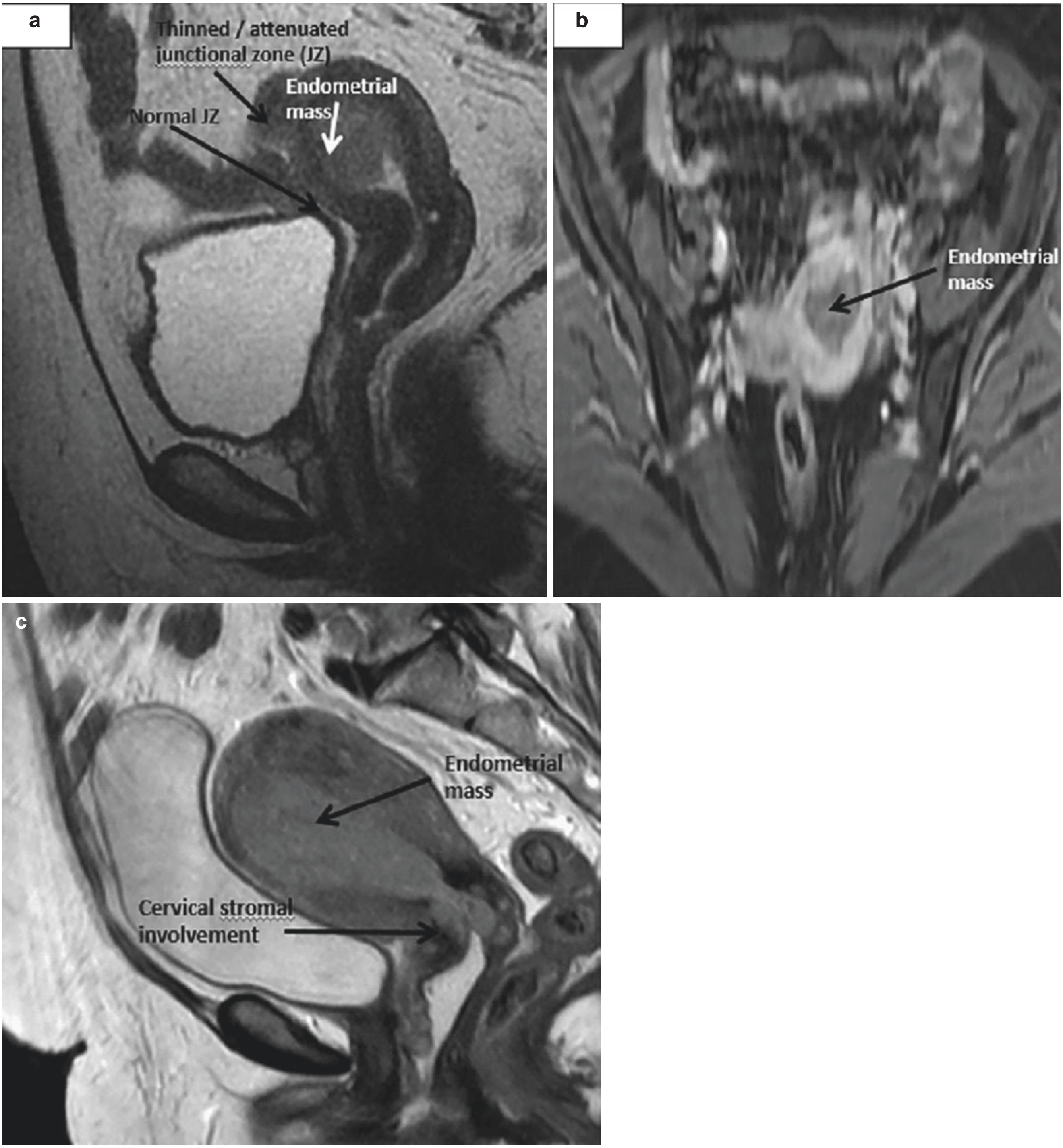
a
Thinned / attenuated junctional zone (JZ)
Endometrial mass
Normal JZ
b
Endometrial mass
c
Endometrial mass
Cervical stromal involvement

Fig. 2 (**a**) MRI-T2W sagittal section showing less than ½ of myometrial involvement. (**b**) Post contrast axial scan showing poor enhancement of the endometrial mass. (**c**) T2W sagittal section showing cervical involvement adjunct especially for the assessment of lymph nodal involvement. These modalities include (not limited to) MRI with ultra-small super paramagnetic iron oxide (USPIO) and diffusion-weighted (DW) imaging.

Positron emission tomography/computed tomography (PET/CT) is highly sensitive (51–69%) and specific (90–100%) for detecting lymph nodal involvement and distant metastases in selected high-risk patients with EC [12].

6.1 Genetic Counselling

Genetic risk assessment is recommended for patients with greater than approximately 20–25% chance of having an inherited predisposition to endometrial, colorectal, and related cancers. Revised Amsterdam criteria is most commonly used in patients with endometrial or colorectal cancers.

7 Staging (Table 1) [13]

7.1 Principles of Management

Comprehensive surgical staging for early-stage endometrial cancer includes peritoneal cytology, total hysterectomy with bilateral salpingooophorectomy with or without pelvic/para-aortic lymph node dissection followed by adjuvant radiotherapy with or without chemotherapy depending on the patient profile and histopathological parameters. Conservative management for fertility preservation may be adopted in young patients with early-stage cancer endometrium with proper counseling and strict follow-up protocols. Surgical staging can be accomplished by laparotomy or laparoscopy. Robotic surgery is an emerging minimally invasive treatment modality for cancer endometrium. The first joint ESMO-ESTRO-ESGO consensus conference on endometrial cancer and the working group has laid down recommendations for management of EC [14].

7.1.1 Fertility-Preserving Treatment

Approximately 4% of cancer endometrium present before 40 years of age. Younger patients present with an early stage favorable histology and have a better prognosis after treatment than their older counterparts.

As per the consensus conference recommendations [14], conservative management of endometrial cancer can be considered in young patient less than 40 years of age with atypical hyperplasia (AH)/endometrial intraepithelial neoplasia (EIN) which are premalignant conditions or stage IA grade 1 endometroid endometrial carcinoma (EEC) confined to the endometrium, at specialized centers. The patient should be counselled pretreatment that the intended treatment is not a standard modality, that she has to adhere to strict follow-up protocols and she may require hysterectomy anytime during treatment or follow-up with risks and benefits of the treatment modality explained. The endometrial biopsy sample should be collected preferably by dilation and curettage with or without hysteroscopy which is considered superior to pipelle in ascertaining grade. The biopsy samples should be examined by specialist gyneconcopathologist. Pretreatment MRI or USG by expert sonologist should be performed to exclude myometrial invasion and adnexal involvement. The medical treatment given is medroxyprogesterone acetate (400–600 mg/day) or megesterol acetate (160–320 mg/day). The response rates for EC are approximately 75%, and recurrence rate is 30–40% [15]. Some papers on LNG IUS and gonadotropin-releasing hor-

Table 1 FIGO 2009 staging (adapted from Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet. 2009 May;105(2):103–4. doi: 10.1016/j.ijgo.2009.02.012. Erratum in: Int J Gynaecol Obstet. 2010 Feb;108(2):176. PMID: 19367689.) [13]

Stage		pTNM	Definition
I			Tumor confined to the uterine corpus ,
	IA	pT1a	No or less than half myometrial invasion
	IB	pT1b	Invasion equal or more than half of the myometrium
II		pT2	Tumor invades cervical stroma but does not extend beyond uterus
III			Local and/or regional spread of the tumor .
	IIIA	pT3a	Tumor invades serosa of the uterus and/or adnexae
	IIIB	pT3b	Vaginal and/or parametrial involvement
	IIIC		Metastases to pelvic and/or para-aortic lymph nodes
	IIIC1	pN1	Positive pelvic nodes
	IIIC2	pN2	Positive pars-aortic nodes with or without positive pelvic nodes
IV .			Tumor invades bladder and/or bowel mucosa; distant metastases
	IVA	pT4	Tumor invasion bladder and/or bowel mucosa
	1VB	pM1	Distant metastases incl. intra-abd. metastases and/or inguinal nodes

mone (GRH) analogues have documented similar results and recurrence rates. The patient is followed up after 6 months with repeat dilation and curettage and endometrial biopsy along with imaging. If the results do not show any treatment response further conservative management is abandoned and hysterectomy is advised. If there is complete response, the patient is referred to infertility specialist. If she wants to postpone pregnancy, she is put on maintenance progestin treatment with 6 monthly follow up as advised. After completion of childbearing hysterectomy with salpingoophorectomy is advised. Ovaries can be preserved in young patients after exclusion of synchronous ovarian malignancy or ovarian metastasis or if she does not have a hereditary predisposition, but salpingectomy should be performed. Studies have shown ovarian preservation does not impact overall survival (OS) in young patients.

8 Surgical Management

The standard treatment is extra fascial total hysterectomy with bilateral salpingoophorectomy with or without lymph node dissection depending upon the frozen section findings. Surgery can be done by open technique, minimally invasive methods, or vaginal approach.

The largest randomized control trial GOG Study LAP2 compared laparoscopy vs laparotomy for comprehensive surgical staging of early stage (I – IIA) uterine cancer over a period of approximately 9 years [16]. Compared to 909 patients who underwent laparotomy, laparoscopy was initiated in 1682 patients and completed without conversion in 74.2% of patients [16]. The main conversion factors were poor visibility (14.6%), metastatic cancer (4.1%), bleeding (2.9%), and other causes (4.1%). Laparoscopy had significantly lesser moderate-to-severe postoperative adverse events but similar intraoperative complication rates. The median operative time was significantly higher in the laparoscopic arm (204 vs. 130 min), but the period of hospital stay was significantly lesser. Pelvic and paraaortic lymph node dissection was not carried out in 8% of patients in the laparoscopy arm as compared to 4% in the laparotomy arm which was statistically significant. Detection of metastatic disease was similar in both arms. So the authors concluded that laparoscopy is a safe and feasible option in terms of short-term outcomes, complication rates, and hospital stay in the management of EC. The major shortcoming appeared to be higher conversion rate owing to multicentric design and variable learning curve of surgeons. Long-term outcomes of the study were published in 2012 with a primary objective to establish noninferior recurrence-free interval with laparoscopy compared to laparotomy with a median follow-up of 59 months [17]. Though the estimated hazard ratio for laparoscopy was 1.14 (lower 90% confidence limit, 0.92; upper 95% confidence limit, 1.46) it fell short of protocol specified definition of noninferiority (lower bound of 1.0, upper bound of 1.4). The actual recurrences rates were lower than anticipated, with 3 years recurrence rates of 10.24% in the laparotomy arm compared to 11.39% in the laparoscopy arm and 5-year recurrence rates of 11.61% and 13.68% for laparotomy and laparoscopy, respectively. At the time of design of the study, with an expected recurrence rate of 15% with laparotomy, the acceptable upper limit of recurrence for laparoscopy was assumed 20.3% after 3 years. The 5-year OS was 89.8% in both arms. Thus, the authors concluded that apart from superiority in short term safety and length of hospital stay outcomes, the potential for increased cancer recurrence with laparoscopy is quantified to be small and can be reasonably useful in patient management of early stage uterine cancers with proper information. A meta-analysis of four RCTs by Palomba et al. [18] concluded no significant difference in OS, DFS, and cancer-related survival between laparoscopy and laparotomy though in the laparoscopic arm, longer operating times, lesser blood loss, and lesser rates of intraoperative complications was seen and there was no difference in pelvic/paraortic nodal yield. Significantly longer operative time but with low blood loss and low rates postoperative complications, similar intraoperative complications without any effect on pelvic/paraaortic nodal yield. Thus, laparoscopy can be regarded as a safe and effective management modality in early-stage EC. In patients who are not physically fit to undergo laparotomy or laparoscopy due to medical conditions or in certain low-risk EC which do not require lymphadenectomy, vaginal hysterectomy with bilateral salpingoophorectomy is an acceptable option. Alternatively, unfit patients can be treated by radiotherapy or hormone therapy.

Robotic surgery is an emerging minimally invasive modality and useful especially in obese patients.

8.1 Role of Lymphadenectomy

The role of lymphadenectomy has been a matter of debate over the past two decades. The crux of the matter is to characterize judicious lymph node dissection. Systematic lymphadenectomy has got its disadvantages and complications; however, it properly stages and prognosticates the disease and guides adjuvant management. Omitting lymphadenectomy understages the disease and subjects the patient to overtreatment with radiotherapy and chemotherapy.

There are various studies in the literature advocating for and against systematic lymph node dissection. Notable studies advocating against lymph node dissection in EC are A Study of Endometrial Cancer (ASTEC) [19] and the Italian study by Panici et al. [20]. Both of these studies concluded the lack of disease free or overall survival advantage by pelvic lymph node dissection in early-stage endometrial cancer. Though both of these were prospective randomized trials, they are criticized by the faulty trial designs and including low-risk endometrial cancers only. Lymph node yield in the ASTEC was low. The benefits of pelvic lymphadenectomy were not used to guide adjuvant treatment in either study. Systematic paraaortic lymph node dissection was not done in either of the trials. It should be emphasized that isolated paraaortic metastasis occurs to the extent of 12.5% Stage IB Grade II and 27% in Stage IB grade 3 disease, respectively. Several retrospective studies have demonstrated survival advantage of systematic pelvic and paraaortic lymph node dissection in intermediate and high-risk endometrial cancers. Notable is the SEPAL (survival effect of para-aortic lymphadenectomy in endometrial cancer). The results showed a significant longer OS in pelvic and paraaortic lymphadenectomy group than in pelvic lymphadenectomy alone in the intermediate- and high-risk group; however, OS was not related to lymphadenectomy in low-risk group [20].

The salient features related to systematic lymphadenectomy in EC as per the ESMO-ESTRO-ESGO Consensus conference recommendations can be summarized as follows:

If indicated, systematic lymphadenectomy includes pelvic and paraaortic lymph node dissection until the level of renal vein.

Systematic lymphadenectomy guides future adjuvant treatment.

Lymph node yield >10–11 is termed adequate.

Low-risk group—Stage IA grade 1/grade 2 endometroid cancers—Lymphadenectomy is not indicated.

Intermediate-risk group—Stage IA G3, IB Grade 1/grade 2 endometroid cancers—Lymphadenectomy may be considered as it helps in staging procedure though survival benefit has not been demonstrated.

High-risk group—Stage IB grade 3 endometroid cancers—Lymphadenectomy is indicated.

For nonendometroid histology apparent stage I disease, i.e., serous, clear cell, undifferentiated and carcinosarcoma, lymphadenectomy is indicated. Omentectomy is an additional staging procedure in serous cancers.

For incompletely staged high-risk cases, complete staging to be done prior to adjuvant treatment.

For stage II disease—Extrafascial hysterectomy with BSO with systematic lymphadenectomy is indicated.

(A Japanese study demonstrated no survival benefit with radical hysterectomy compared to simple hysterectomy in stage II EC. However, radicality may be adopted in individual circumstances to get free margins if parametria is involved.)

8.2 Role of Sentinel Lymph Node Mapping in EC

Sentinel lymph node is the first lymph node that is involved in the pathway of cancer metastasis via the lymphatic route. If the sentinel node is negative, it is surmised that the rest of the lymph nodes are not involved. Of the two studies, the SENTI ENDO study and the FIRES (Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy) trial [21], notable is the FIRES trial which was a prospective multicenter cohort study to evaluate the sensitivity and negative predictive value of sentinel lymph node mapping in stage 1 disease of all histologies undergoing robotic surgical staging as compared to complete lymphadenectomy which is the gold standard. Indocyanin green dye was injected into cervix (0.5 mg/mL) after anesthesia and sentinel lymph node was picked up by fluorescence imaging. The procedure has a sensitivity of 97.2% (95% CI 85.0–100) to detect node-positive disease with a negative predictive value of 99.6%. Thus, the authors concluded that the method has a high diagnostic accuracy in detection of lymph node metastasis.

For advanced stage ECs, multimodality treatment is preferred. The aim of surgery is comprehensive staging with optimal cytoreduction.

9 Pathology

Endometrioid adenocarcinoma is the most common histologic subtype comprising 75–80% of all ECs. Marked glandular proliferation with minimal intervening stroma is the typical histological appearance and resembles proliferative phase endometrium. Architectural grading is based on the amount of nonsquamous or solid component with grade I being formed by <5%, grade II ranging from 6 to 50% and grade III having more than 50% nonsquamous or solid growth pattern. Other histologic subtypes seen include uterine papillary serous, clear cell, mucinous, squamous cell carcinoma, transitional cell carcinoma, and mixed cell-type carcinoma.

9.1 Pathological Reporting

The Royal College of Pathologists has published guidelines for the pathological reporting of hysterectomy specimens for EC [21]. Core data items to be included in the report are

(a) Hysterectomy type
(b) Details of hysterectomy specimen—The different components of the specimen (uterine corpus, cervix, ovaries, and tubes) should be specified and macroscopic appearance recorded. The presence of a vaginal cuff and

of parametrial tissues should be recorded in case of radical hysterectomy specimens.

(c) Accompanying specimens—Omentum, if received, should be recorded. Number of lymph nodes from each site and peritoneal biopsies should be described.
(d) Gross tumor details—The gross appearance of the tumor including dimension, presence of gross myometrial invasion, cervical involvement, parametrial involvement, or serosal surface involvement
(e) Tumor type
(f) Tumor grade
(g) Depth of myometrial invasion
(h) LVSI
(i) Cervical stromal invasion
(j) Vaginal involvement
(k) Uterine serosal involvement
(l) Parametrial involvement
(m) Adnexal involvement
(n) Omental involvement
(o) LN involvement
(p) Peritoneal involvement
(q) Provisional FIGO stage

Non-core data items to be included are

(a) Specimen weight and measurements
(b) Location of tumor

10 Radiation Management

10.1 Risk Stratification

Multiple clinicopathologic factors have been evaluated based on which patients are divided into risk groups. Like most risk groupings across sites, this risk stratification also guides prognosis as well as the use of adjuvant therapy. Established prognostic factors include age, FIGO stage, depth of myometrial invasion, tumor differentiation grade, tumor type (endometrioid vs. serous and clear cell), and lymphovascular space invasion (LVSI). The latest risk stratification divides subgroups into low-risk, intermediate-risk, high-intermediate risk, and high-risk groups (Table 2) [14, 15].

The addition of molecular-based classification is particularly relevant as POLE mutant tumors are known to have an excellent prognosis, while p53 abnormal tumors have a poor prognosis. Another update in the risk stratification is the subdivision of LVSI into focal and substantial [15].

10.2 Low-Risk Endometrial Cancer

For patients with low-risk endometrial cancer, the risk of recurrence after surgery alone is less than 5%. Some patients which are considered as low risk as per the current risk stratification were previously included in randomized trials of adjuvant RT. There was no benefit of adjuvant RT for this subgroup. Another randomized trial by Sorbe et al. [22] for patients with low-risk EC (N = 645) treated with vaginal brachytherapy (VBT) also failed to show any benefit for the use of adjuvant brachytherapy. There have also been reports of increased toxicity, especially long-term gastrointestinal toxicity with the use of adjuvant radiotherapy (RT) without any benefit in terms of overall survival (OS) or reduction in distant metastases [23]. Therefore, patients with low-risk EC can be observed following surgery.

Table 2 ESMO-ESGO-ESTRO-ESP classification of risk groups for adjuvant therapy [14, 15]

Risk group	Molecular information	Histopathological features
Low risk	POLE mut	Stages I & II
Intermediate risk	MMRd/ NSMP	Stage IA, Low grade, LVSI −ve/ focal
High-intermediate risk	MMRd/ NSMP	Stage IB, Low grade, LVSI −ve/ focal
High risk	MMRd/ NSMP	Stage III–IVA with no residual disease Stage I–IVA Non EC with myometrial invasion
	p53 abn	St I-IVA with myometrial invasion (EC + Non EC) with no residual disease
Metastatic	Any molecular type	Gross residual disease

Stage I-II EC with POLE mutations have demonstrated excellent local control rates and do not require any adjuvant treatment. For stage III EC with POLE mutations, data is available from PORTEC-3 trial which showed excellent outcomes. However, since patients in both the arms received EBRT, the effect of omitting adjuvant treatment is difficult to quantify.

10.3 Intermediate-Risk Endometrial Cancer

Multiple randomized trials assessing the role of adjuvant RT in early-stage EC included patients who are currently classified as being in the intermediate-risk group. These trials (MRC ASTEC, PORTEC-1, NCIC CTG EN.5, GOG-99) [20, 24–26]) randomized patients after surgery (TAH + BSO) to either pelvic external beam radiation therapy (EBRT) or observation. All these trials and a meta-analysis [26] showed that EBRT reduced the risk of pelvic recurrence by threefold without any significant OS benefit. Lower pelvic recurrence rates, however, came at the cost of increase in GI toxicity. GOG-99 in contrast to PORTEC-1 mandated staging lymphadenectomy, emphasizing the role of EBRT even for node-negative disease. The reduced risk of recurrence in this case was mainly owing to reduction in vaginal recurrences.

Table 3 compares randomized trials of adjuvant RT with observation in early endometrial cancer.

Greatest benefit of RT was seen in a select subgroup of patients which forms the high-intermediate risk group. PORTEC-1 defined risk groups as age >60 years, >50% myometrial invasion and grade 3 differentiation, with the high-intermediate risk group having at least 2 of these characteristics. Patients in this subgroup who received adjuvant RT had a 5-year risk of locoregional recurrence (LRR) of 5% as compared to 20% for those who were observed. The risk of LRR was deemed high enough only in this subgroup for adjuvant RT to be considered.

The PORTEC-2 trial included only patients with the high-intermediate-risk factors defined in PORTEC-1 and randomly assigned patients to either adjuvant pelvic EBRT or VBT. There was no significant difference in the rates of vaginal recurrence (1.8% vs 1.6% for VBT and EBRT respectively, HR 0.78, 95% CI 0.17–3.49; $p = 0.74$) or pelvic recurrence (5.1% vs 2.1% for VBT and EBRT respectively, HR 2.08, 0.71–6.09; $p = 0.17$) between the two arms. Rates of acute GI toxicity were significantly lower with VBT as compared to EBRT with a better quality of life in favor of VBT [27].

LVSI and grade 3 differentiations have been identified as risk factors for disease recurrence by multiple studies, and these findings were confirmed in pooled analysis of PORTEC-1 and 2 which showed increased risk of nodal and distant recurrences in this subgroup of patients [28]. EBRT decreased the risk of regional nodal recurrence in this small subgroup (5%) of patients, while VBT did not.

The above stated studies were not adequately powered to show statistically significant OS benefit.

The pooled analysis of PORTEC 1 and 2 has enabled the development of nomograms which guide the assessment of risk and predict the benefit of adjuvant RT for patient subpopulations [29].

Data from the PORTEC-2 trial also showed that with VBT alone only a small number of patients had a higher risk of pelvic relapse based on substantial LVSI, p53abn, and L1CAM overexpression and hence only focal LVSI and no p53abn are included in intermediate-risk category.

In patients with intermediate-risk EC (stage I endometrioid, grade 1–2, >50% myometrial invasion, LVSI-negative), adjuvant VBT is recommended to decrease vaginal recurrence. If EBRT is considered, it should be delivered with small portals, restricted to the mini-pelvis. Patients need to be explained the potential risk of higher GI toxicity with EBRT. Observation is an option especially for patients younger than 60 years of age.

10.4 High-Intermediate-Risk Endometrial Cancer

The GOG 99 and PORTEC 1 trials reported a significant reduction in LRR from 26% to <6% and >20% to 5%, respectively; however, neither showed any difference in OS (both trials underpowered for OS end-point).

For this group of patients, the use of adjuvant RT, whether VBT or EBRT, is controversial. Various factors like intraoperative information, histopathological risk factors, and type of surgery are taken into account before making a decision. This notwithstanding, most older patients with tumor features of LVSI and high-grade differentiation tend to be treated with EBRT irrespective of lymph nodal dissection. Node-negative patients can be treated with mini-pelvic fields to avoid excess GI toxicity. VBT alone is sufficient for patients with deep myometrial invasion without LVSI. If LVSI is indeterminate, then it is better to err on the side of caution and treat with EBRT [30].

10.5 High-Risk Endometrial Cancer

High-risk endometrial cancer is a heterogeneous group formed by both endometrioid and nonendometrioid histologic subtypes and is associated with an increased risk of pelvic recurrence and distant metastases. It is also important to understand that the spectrum of patients in the high-risk group is wide in terms of the stage of disease ranging from IB Grade 3 to more advanced stages. Nonendometrioid tumor types have a high percentage of extrauterine disease at presentation (60–70%). Patients with uterine serous cancer have a 5 year OS of about 20–25% as compared to 80% for all patients with endometrial cancer.

The estimated 5-year OS is 85–90% for stage I, 75–85% for stage II, 50–65% for stage III, and 20–25% for stage IV [14].

Due to this overwhelming heterogeneity, separate recommendations have been made for the following subgroups:

Table 3 Comparison of randomized trials of adjuvant RT with observations in early endometrial cancer

	LN Dissection	VBT	LRR	OS
PORTEC-1	NO	NO	4%(RT) vs 14%(NAT), $p < 0.001$	81% vs 85%, $p = 0.31$
GOG 99	MANDATORY	VBT	3% (RT) vs 12% (NAT), $p = 0.007$	92% vs 86%, $p = 0.557$
ASTEC/EN.5	29% patients	Allowed	4% vs 7%	85% in both arms

Endometrioid stage I, grade 3 and >50% myometrial invasion; endometrioid stage II; endometrioid stage III without residual disease and nonendometrioid tumor types.

For high-risk patients, standard of treatment remains pelvic EBRT. Two randomized trials (NSGOEC-9501/EORTC-55991 and MaNGO ILIADE-III) were conducted to evaluate the role of sequential combination of chemotherapy and radiotherapy in high-risk EC.

Hogberg et al. published the pooled analysis of these two studies which reported that the addition of adjuvant chemotherapy (4 cycles of platinum-based chemotherapy given either before or after RT) to EBRT led to a significant improvement in 5-year progression-free survival (78% vs. 69%, $P = 0.009$) and a trend toward improved OS (82% vs 75%, $P = 0.07$). Subgroup analysis from the study showed that the benefit was seen only in endometrioid histology; however, owing to the unplanned nature of the analysis and the small sample size, no clear conclusions can be drawn for it [31].

The PORTEC-3 trial (adjuvant EBRT alone vs. EBRT with concurrent and adjuvant chemotherapy) reported a significant improvement in 5-year OS (81.4% vs. 76.1%; $p = 0.034$) and failure free survival (FFS) in favour of chemoradiotherapy (76.5% vs. 69.1%; $p = 0.016$) (2 cycles concurrent with radiation followed by 4 cycles of chemotherapy) as compared to pelvic radiotherapy alone. Subgroup analysis revealed that the benefit was significant in more advanced/aggressive disease with 11% FFS benefit and OS benefit in patients with stage III disease, non-endometrioid histology and patients older than 70 years of age. However, as expected, the addition of chemotherapy resulted in significantly higher grade 2 and above toxicities [32].

The GOG-258 trial compared the same chemotherapy-radiotherapy schedule used in PORTEC-3 with six cycles of carboplatin-paclitaxel chemotherapy alone and found overlapping relapse-free and overall survival rates. However, the chemotherapy alone arm had significantly higher rates of pelvic and peri-aortic nodal relapse.

Molecular analysis of PORTEC-3 trial showed statistically significant survival advantage for p53abn carcinomas with combined therapy for stages I–III. In contrast, *POLE*mut carcinomas had almost no recurrences in both arms. There was no clear benefit of added chemotherapy for MMRd, while the NSMP carcinomas had some benefit of added chemotherapy especially in case of stage III.

Adjuvant therapy for patients with high-risk node negative EC (stage I endometrioid, grade 3, >50% myometrial invasion, regardless of LVSI status) with adequate surgical nodal staging should include adjuvant EBRT with small portals. However, VBT may be considered as an alternative in select cases. For patients who have not undergone surgical nodal staging, pelvic EBRT should be given with or without adjuvant chemotherapy.

10.6 High-Risk, Stage II Endometrial Cancer

The definition of stage II was modified in the 2009 FIGO staging system. Endocervical glandular involvement was moved to stage I as it has no prognostic impact. A SEER analysis was carried out for stage II endometrial cancer patients in who almost half had cervical stromal involvement. This analysis did not show any difference in OS for the type of surgery that was performed in terms of radical or simple hysterectomy but RT independently of surgery was associated with survival benefit [33]. There is a lack of consensus as to the role of VBT boost in combination with EBRT. In case of positive vaginal margin, indication of VBT is clear. Studies have not found a clear difference in LR or OS rates for stage II patients treated with or without VBT in addition to EBRT.

In patients who are node negative upon a thorough surgical staging, EBRT with mini pelvic fields (with or without VBT boost) is recommended only for high-grade tumors or those with LVSI, while VBT is sufficient for lower grade without LVSI. For patients who have not undergone a thorough surgical nodal staging, pelvic EBRT with VBT boost is recommended with the addition of chemotherapy for high-grade tumors or those with LVSI.

10.7 High-Risk, Stage III Endometrial Cancer

Secord et al., in a retrospective analysis, showed that for patients with stage IIC endometrial cancer survival was worst in those who received adjuvant chemotherapy alone as compared to those who received either RT alone or combined RT and chemotherapy. Relapse-free survival was similar in patients receiving RT alone or in combination with chemotherapy [34]. Therefore, pelvic and/or extended field RT remains standard of care in this group of patients. In light of results of the trials already mentioned afore combined radiation therapy with chemotherapy is recommended as opposed to either alone.

In patients with high-risk, stage III endometrial cancer without residual disease, EBRT and chemotherapy in combination are recommended with extended field EBRT reserved for stage IIC2 disease.

10.8 High-Risk, Non-Endometrioid Cancers

These are rare tumors hence most studies are retrospective and comprise of small number of patients. A large retrospective study conducted by Viswanathan et al. suggested a survival benefit for the combination of chemotherapy and RT in uterine serous cancer [35]. However, as mentioned earlier, a subgroup analysis of the NSGOEC9501/EORTC 55991 and

MaNGO-ILIADE III trials did not show a survival benefit for serous or clear cell tumors. Since there is a high rate of distant metastases associated with these high-risk nonendometrioid histologies, adjuvant chemotherapy should be considered and clinical trials are encouraged.

Retrospective studies have investigated the role of VBT. One such study was conducted in patients of stage I serous or clear cell cancers. Of note, 34% patients included in the study also received adjuvant chemotherapy. The 5-year rate of isolated pelvic recurrence and LRR was 4% and 7%, respectively, with a 5-year OS rate of 84%, suggesting that VBT alone is sufficient in patients with stage IA disease [36].

Carcinosarcomas are rare and aggressive tumors with a large proportion of patients presenting with extrauterine disease at diagnosis. The 5-year OS for patients with stage I disease is a mere 50%. The EORTC-55874 trial randomized patients with stage I-II uterine sarcomas ($n = 224$) to either observation or pelvic RT (51 Gy/28 fr over 5 weeks) after surgery. About 40% of the patients on the study had carcinosarcoma. Adjuvant RT significantly reduced the risk of local relapse without any impact on OS or the rate of distant metastasis [37].

For all non-endometrioid histologies, adjuvant chemotherapy is recommended. For patients with serous and clear cell histology who have undergone thorough surgical staging, VBT alone is sufficient for selected early stage tumors (stage IA without LVSI). For stage IB or higher or patients with carcinosarcoma, pelvic EBRT should be considered.

11 Medical Management

The standard surgical management for EC leads to permanent loss of reproductive potential. A select group of patients in the reproductive age group and desirous of preserving fertility may be managed conservatively using oral progestins. Patients who are diagnosed with endometrial hyperplasia or FIGO stage IA Grade I endometrial cancer may be offered this approach. It is essential that MRI be used as part of the diagnostic work up to rule out deep myometrial invasion. The grade should be confirmed on D and C, and a mere office biopsy is not sufficient. The patients should be carefully selected and must be informed that this is nonstandard treatment, and they must be willing for close follow-up and may require to undergo hysterectomy in the future.

Medroxyprogesterone acetate (MPA) 40–600 mg/day or megesterol acetate 160–320 mg/day may be used. As an alternate, the use of LNG-IUD in addition to GnRh analogs has also been described, and the results in terms of response rates and recurrences are similar to that of oral progestins. Response is assessed at 6 months after therapy with repeat imaging and dilatation and curettage. About 75% of patients do respond, but there is also a high recurrence rate of 30–40%. If the patients respond, then maintenance therapy is continued for another 6 months otherwise patient is taken up for hysterectomy.

Chemotherapy is not recommended for patients in the low- or intermediate-risk group.

11.1 High-Intermediate Risk

The GOG 249 study investigated the role of chemotherapy in high-intermediate risk and high-risk patients. Patients were randomized to either pelvic EBRT or VBT followed by adjuvant chemotherapy (3 cycles of paclitaxel and carboplatin). The addition of chemotherapy did not result in improvement of either relapse-free survival or OS. In fact, there was a higher risk of pelvic and para-aortic nodal recurrence in the VBT and chemotherapy arm (9.2% vs. 4.4% at 5 years) [38].

11.2 High-Risk Patients

Many studies have attempted the addition of chemotherapy to RT or tried to substitute RT with chemotherapy for high-risk patients.

JGOG 2033 study randomized patients to pelvic EBRT vs. three cycles of adjuvant CAP chemotherapy (cyclophosphamide-adriamycin-cisplatin). The study found no difference in DFS and OS between the two arms [39].

As eluded to earlier, the pooled analysis of NSGOEC-9501/EORTC-55991 and MaNGO ILIADE-III showed a significant improvement in 5-year PFS and a trend to improvement in OS on addition of chemotherapy to RT.

The PORTEC-3 trial, as eluded to earlier, was initiated to evaluate the benefit of adjuvant chemotherapy during and after RT versus pelvic RT alone for women with high-risk EC. Patients with high-risk EC were randomized to receive RT alone versus concomitant chemoradiotherapy (two cycles cisplatin given during RT) followed by 4 cycles of carboplatin and paclitaxel. As seen with other studies, the combined chemotherapy and radiotherapy arm did not improve 5-year OS but showed an improvement in failure-free survival.

The GOG 258 trial in high-risk stage III / IVa disease compared adjuvant chemoradiotherapy and chemotherapy alone. Chemoradiotherapy consisted of 2 cycles of concomitant cisplatin with RT (intensity-modulated RT and VBT allowed) followed by 4 cycles of paclitaxel and carboplatin as opposed to 6 cycles of paclitaxel and carboplatin in the chemotherapy alone arm. The primary end point of the study, relapse-free survival showed no improvement with the addition of RT as compared to chemotherapy alone. In the chemotherapy alone arm, there were higher vaginal and nodal recurrences, whereas distant metastases were higher in the chemoradiotherapy arm [40].

For high-risk non-endometrioid histology, most of the evidence as mentioned is retrospective and small patient numbers. But in view of the high rate of distant metastases, chemotherapy is recommended in this subset of patients.

12 Advanced and Recurrent Disease

Surgery is preferable for patients with advanced (bulky IIIA/IV) or recurrent disease but should be performed only when complete cytoreduction without macroscopic residual disease can be achieved. Evidence from meta-analysis of 672 patients has shown patients who undergo complete cytoreduction [41]. Exenteration is also an option for patients with advanced disease and central relapse.

For early-stage endometrial cancers especially grade I/II without LVSI or deep myometrial invasion are amenable to observation. These patients may end up with isolated vaginal recurrences in which case salvage RT provides good local control. In PORTEC-1, patients with isolated vaginal relapses were treated with radical intent with a combination of pelvic EBRT and VBT with a resulting local control rate of 89% and 79% DFS at a median follow-up of 44 months. Patients who receive adjuvant primary RT are at an increased risk of distant relapses. In these patients, reirradiation may be considered especially with the advent of sophisticated techniques like image-guided intensity-modulated radiotherapy.

The benefit of addition of chemotherapy for patients with vaginal relapses or pelvic nodal recurrences is unclear. GOG 0238 is an ongoing trial that is randomizing patients to EBRT plus VBT versus EBRT boost with weekly cisplatin chemotherapy. The results of this trial should make the picture clearer but for the time being for the patients who are deemed to be at a high risk of systemic relapse, the addition of chemotherapy may be considered.

For patients who present with painful bony metastases or painful nodal recurrences or bleeding, palliative radiotherapy remains an option.

12.1 Systemic Therapy in Recurrent/Metastatic Disease

Thigpen et al. showed that hormone therapy is a viable option with a convenient toxicity profile in patients who have recurrent disease. Hormone therapy is more effective in Grade I/II tumors with response rates of 37% in grade I, 23% in grade II, and only 9% in grade III tumors [42]. For patients whose disease is not surgically resectable nor amenable to radiotherapy, hormonal therapy is a good first-line option if disease is not rapidly progressive. In case of rapidly progressive disease, systemic chemotherapy needs to be considered.

Clinical trials have shown that objective response rates are higher for combination of cisplatin and doxorubicin than doxorubicin alone. A GOG trial showed that the addition of paclitaxel to cisplatin and adriamycin (TAP regimen) significantly improved median PFS (8.3 mo vs. 5.3 mo) and OS (15.3 mo vs. 12.3 mo), but this improvement came along with an increase in the toxicity as well as a result of which the TAP regimen has not been adopted as a standard of care [43].

GOG 209 was a non-inferiority trial which randomized patients to receive TAP-based chemotherapy vs a combination of paclitaxel and carboplatin every 3 weeks. The PFS in the two treatment arms was similar and the TC arm had a non-inferior OS. The TC arm had a definite advantage in terms of toxicity profile and also TC can be administered on outpatient basis, whereas the TAP regimen is usually administered with the patient admitted [44]. As a result, TC has now been adopted as the regimen of choice for recurrent/metastatic disease. There are no randomized data for second-line chemotherapy, though.

Many newer targeted agents have also been evaluated of which the most promising seems to be bevacizumab. In the MITO-END 2 trial, bevacizumab was added to 6–8 cycles of TC followed by maintenance therapy significantly improved PFS (13 mo vs. 8.7 mo) [45].

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Cervical Cancer

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Abbreviations

3D CRT	Three-dimensional conformal radiation
APC	Argon plasma coagulation
ARV	Antiretroviral therapy
BT	Brachytherapy
CIN	Cervical intraepithelial neoplasia
CT	Computed tomography
EAC	Endocervical adenocarcinoma
EBRT	External beam radiation therapy
EUA	Examination under anesthesia
FNAC	Fine-needle aspiration cytology
FDG	18-Flouro-deoxyglucose
GAC	Gastric type mucinous adenocarcinomas of the cervix
HPV	Human papilloma virus
HPVA	HPV-associated LEEP loop electrocautery excision procedure
IECC	International Endocervical Adenocarcinoma Criteria and Classification
IGABT	Image-guided adaptive BT
IGRT	Image guidance radiation therapy
IMRT	Intensity-modulated radiation therapy
LMIC/LIC	Low–middle-income/low-income countries
LVSI	Lymphovascular space invasion
MRI	Magnetic resonance imaging
NHPVA	Non-HPV-associated
OAR	Organs at risk
OLM	Oligometastases
OS	Overall survival
OTT	Overall treatment time
PDR	Pulse dose rate
PET	Positron emission tomography
PFS	Progression-free survival
PID	Pelvic inflammatory disease
QOL	Quality of life
RR	Response rates
SBRT	Stereotactic body radiotherapy
VMAT	Volumetric arc therapy

1 Introduction

Cervical cancer continues to present as a challenge to gynecological oncologists considering large number of women who die annually of the disease. The presentation of cervical cancer differs in the developed and the developing world. Early stage disease constitutes 60% to 70% of patients in the developed world contrary to three-fourths presenting as locally advanced disease in low–middle-income/low-income countries (LMIC/LIC). The recent declining incidence of cervical cancer across the globe can be attributed to improving living standards and widespread screening strategies. This chapter briefly summarizes the management of cervical cancer from evaluation to treatment, highlighting the protocol followed at Tata Memorial Centre.

2 Incidence and Epidemiology

Cervical cancer is the fourth most common cancer among women worldwide with an estimated new case load of 569,847 and 311,365 deaths across the globe (GLOBOCAN 2018). In India, it is the second leading cause of female cancers after breast cancer with age standardized incidence rate of 14.7 per 100,000 women. Annually, India has new 96,922 cases with

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60,078 cervical cancer deaths as estimated in 2018. The age-standardized mortality rate is 9.2 per 100,000 women per year in India as compared to the global rate of 6.9 [1].

3 Clinical Presentation

In an early stage, patients may be asymptomatic and cervical cancer discovered incidentally during screening. Postcoital bleeding is the most common presentation. Other presentations may include foul-smelling blood tinged discharge, intermenstrual bleeding or postmenopausal bleeding. In late advanced stages, pelvic pain, urinary and bowel symptoms related to invasion or obstruction may be present. In cases with distant metastases shortness of breath, headache, seizures and bone pain may present as per the organ of spread.

4 Evaluation and Work-Up

Complete physical and pelvic examination is a must for clinical evaluation and staging of patients presenting with cervical cancer. A directed punch biopsy is taken for confirmation of diagnosis. In a very small lesion or with negative biopsy in a highly suspected case, colposcopic-guided biopsy is appropriate. Pelvic examination should entail detailed per-speculum, per-vaginal and per-rectal examinations. In cases of doubtful parametrial involvement or a noncooperative patient, examination under anesthesia (EUA) is done. At present, no tumor markers have been proven to be useful for evaluation or during follow up in cases of cervical cancer. Chest X-ray is used for staging purposes. The imaging modalities that are used are an ultrasound scan, computed tomography (CT) and magnetic resonance imaging (MRI). In resource strained settings, a good sonogram with high resolution probe can suffice. Information via sonogram can be gathered by abdominal, transvaginal and transrectal approaches. T2-weighted MRI is the modality of choice as it is superior in demarcation of growth, parametrial involvement and extent of involvement when planning for trachelectomy [2]. For parametrial infiltration, EUA has shown to have a negative predictive value of 65.3% and MRI of 76.9%, respectively [3]. For staging purposes, MRI is superior as compared to CT scan (sensitivity 75% vs. 51%) [4]. Nodal involvement detection is almost similar with MRI and CT imaging (sensitivity 38%–89%; specificity 78%–99%) [5]. FDG-PET imaging seems to be superior in sensitivity, specificity and accuracy for pelvic, para-aortic nodal disease evaluation [6]. Suspicious pelvic or para-aortic nodes on CT or MRI should be confirmed with image-guided fine-needle aspiration cytology (FNAC) or biopsy. Cystoscopy or sigmoidoscopy can be used for cases with suspected bladder or rectal invasion, respectively. The updated FIGO 2018 staging of cervical cancer is given in Table 1 [7]. The revisions essentially include stage IA definitions changes, addition of stage IB3 and including pelvic/para-aortic nodal involvement as a part of staging.

Table 1 FIGO staging of carcinoma of the cervix uteri (2018)

Stage I			The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)
	IA		Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
		IA1	Measured stromal invasion <3 mm in depth
		IA2	Measured stromal invasion ≥3 mm and < 5 mm in depth
	IB		Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri[b]
		IB1	Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension
		IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
		IB3	Invasive carcinoma ≥ 4 cm in greatest dimension
Stage II			The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
	IIA		Involvement limited to the upper two-thirds of the vagina without parametrial involvement
		IIA1	Invasive carcinoma <4 cm in greatest dimension
		IIA2	Invasive carcinoma ≥4 cm in greatest dimension
	IIB		With parametrial involvement but not up to the pelvic wall
Stage III			The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
	IIIA		Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
	IIIB		Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
	IIIC		Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
		IIIC1	Pelvic lymph node metastasis only
		IIIC2	Para-aortic lymph node metastasis
Stage IV			The carcinoma has extended beyond the true pelvis or has involved (biopsy-proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV
	IVA		Spread of the growth to adjacent organs
	IVB		Spread to distant organs

Adapted from [7]

When in doubt, the lower staging should be assigned

[a] Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages

[b] The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered

[c] Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented

5 Pathology

The malignant tumors of the uterine cervix include carcinomas, malignant mesenchymal tumors, mixed carcinomas and mesenchymal tumors, melanomas, hematolymphoid malignancies, germ cell tumors and secondary tumors. The discussion restricted to common epithelial malignancies—carcinomas.

5.1 Squamous Carcinoma

Squamous cell carcinoma of the uterine cervix includes microinvasive and invasive variants that may have different biological behavior such as verrucous, papillary, transitional, lymphoepithelioma, etc.

Microinvasive squamous carcinoma is a squamous carcinoma with early stromal invasion. Microinvasive squamous carcinoma should not be diagnosed on cervical biopsy, and only be diagnosed on large loop electrocautery excision procedure (LEEP) specimen, where the extent of the tumor can be studied in entirety.

An invasive carcinoma composed of squamous cells of varying degree of differentiation. Nearly all cervical cancers are caused by persistent infections by high-risk/carcinogenic human papilloma viruses (HPV), and proportion of squamous histology is approximately 70%. Macroscopically, it may be predominantly exophytic or endophytic. Histology shows irregular, spiked islands, sheets with intervening stroma. Keratin may or may not be seen. Cervical intraepithelial neoplasia (CIN) may be found on its surface or at the edge of the invasive tumor front. Conventionally, a four-tier grading system (Broaders) or a three-tier grading system (well, moderately differentiated, poorly differentiated) is in use; but it has not been proven useful prognostically (Fig. 1i, ii). Only recently, a novel, highly prognostic grading system has been proposed based on tumor budding and cell nest size for squamous carcinoma cervix [8]. A variety of subtypes are described (basaloid, verrucous, warty, squamotransitional, papillary, spindle cell type, lymphoepithelioma, etc.).

Pooled data indicate that a maximum depth of 3 mm or less is associated with a risk of lymph node metastasis of <1%, and a risk of invasive recurrence of 0.9%, while depth of invasion of 3–5 mm is associated with an overall risk of lymph node metastasis of 2% and a recurrence rate of 4% [9].

5.2 Adenocarcinoma

The relative and real incidence of endocervical adenocarcinoma (EAC) has been increasing worldwide, with up to 20–25% of all invasive cervical carcinomas now being assigned to this category [10].

The current World Health Organization (WHO) classification of cervical tumors lists types of cervical adenocarci-

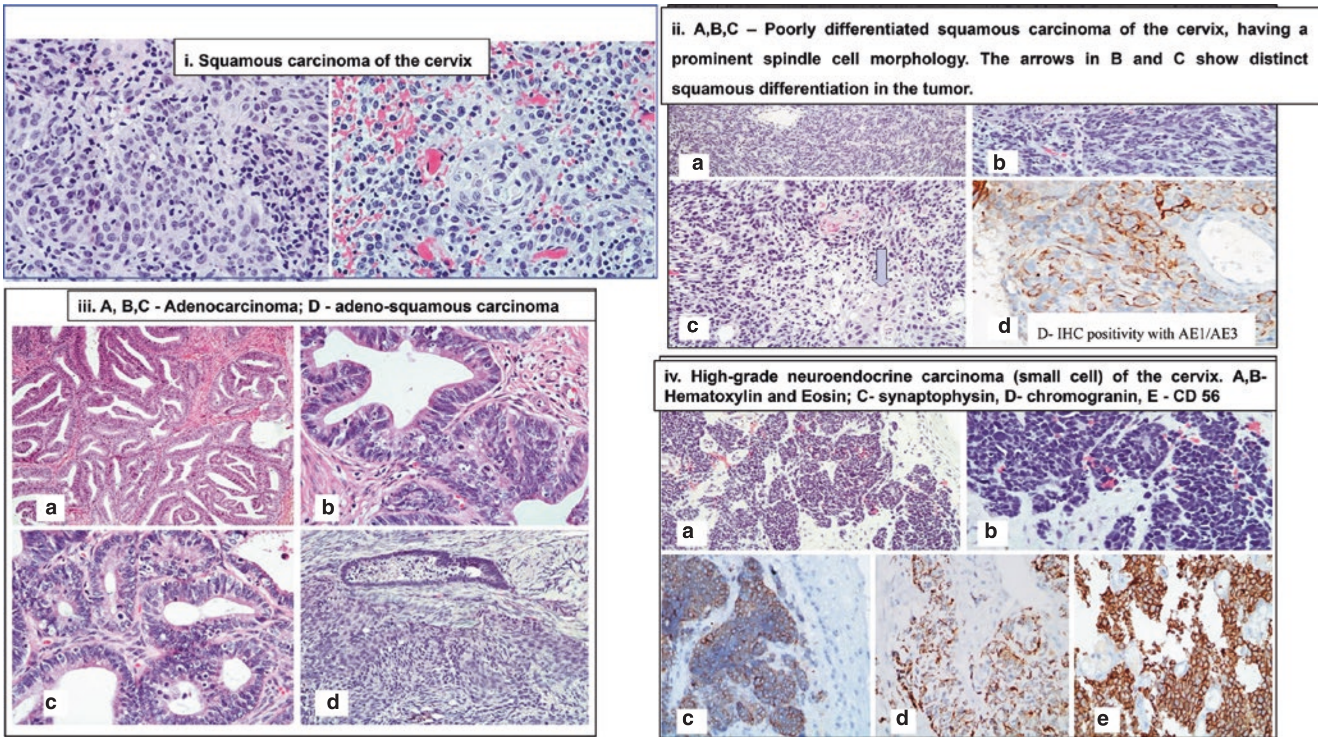

i. Squamous carcinoma of the cervix
ii. A,B,C – Poorly differentiated squamous carcinoma of the cervix, having a prominent spindle cell morphology. The arrows in B and C show distinct squamous differentiation in the tumor.
a
b
c
d
D- IHC positivity with AE1/AE3
iii. A, B,C - Adenocarcinoma; D - adeno-squamous carcinoma
a
b
c
d
iv. High-grade neuroendocrine carcinoma (small cell) of the cervix. A,B- Hematoxylin and Eosin; C- synaptophysin, D- chromogranin, E - CD 56
a
b
c
d
e

Fig. 1 Different histologies and staining characteristics

nomas as usual type of adenocarcinoma, mucinous adenocarcinoma (gastric, intestinal, signet ring type), villoglandular carcinoma, endometrioid carcinoma, clear cell carcinoma, serous carcinoma, adenocarcinoma mixed with neuroendocrine carcinoma, etc. (see Fig. 1iii, iv) [9].

Most mucinous adenocarcinomas are considered to be HPV-associated tumors, but gastric type mucinous adenocarcinomas of the cervix (GAC) are mostly non-HPV-associated. The later show distinct morphological features, gastric phenotype, are HPV DNA negative, are negative for P16 and are positive for MUC6.

Hence, recently, International Endocervical Adenocarcinoma Criteria and Classification (IECC) proposed and showed a reliable segregation of HPV-associated (HPVA) and non-HPV-associated (NHPVA) endocervical adenocarcinoma. The non-HPV-associated tumors include gastric type, endometrioid type, clear cell type, mesonephric type, serous type and invasive adenocarcinoma, NOS [11].

Distinction between HPVA and NHPVA is important given the difference in their pathogenesis and clinical behavior, e.g., the gastric type adenocarcinoma has significantly worse outcome [12].

5.3 Neuroendocrine Carcinomas

Neuroendocrine tumors of the cervix are rare tumors and comprise less than 2% of all invasive carcinomas [13].

In among NET, carcinoid tumors and atypical carcinoid tumors (equivalent to well-differentiated grade 1 and grade 2 NET, respectively) are extremely uncommon in cervix. High-grade neuroendocrine carcinoma (small cell type and large cell type) are well recognized and are aggressive tumors. They are to be suspected when a seemingly poorly differentiated squamous carcinoma starts showing trabeculae or rosettes (see Fig. 1iv). Just like their lung tumor counterparts, they do show crushing artifacts. They are treated with surgery but more often with chemotherapy involving platinum and etoposide.

5.4 Mesenchymal Tumors

These rare tumors that arise from the cervix include leiomyosarcoma, endometrial stromal sarcoma, undifferentiated endocervical sarcoma, embryonal rhabdomyosarcoma, alveolar soft part sarcoma, angiosarcoma, malignant peripheral nerve sheath tumors.

6 Principles of Management

Patients with cervical cancer should ideally be managed in a cancer center with comprehensive cancer care services, which has the required expertise, skills and infrastructure. The primary prevention, screening and management of noninvasive and early micro-invasive cervical cancer (up to FIGO stage IA2) will be dealt in detail and out of scope of the current chapter. The treatment decision for invasive cervical cancer is based on (1) tumor-related factors including staging, histology type, and (2) patient-related factors including age, performance status, comorbidities and most important patient choice if options available. In general, early stage cervical cancers (FIGO stage I–IIA) are treated with radical surgery. Postsurgery based on adverse histopathological features, patients are classified in low, intermediate and high risk to offer adjuvant radio(chemo)therapy. Figure 2 shows the flowchart for diagnosis, evaluation and management principles for cervical cancer utilized at Tata Memorial Centre.

In early invasive cervical cancer (FIGO 2018 stage IB1 and IIA1) the standard of care is either surgery (radical/modified radical hysterectomy) or radiotherapy both of which have equivalent outcomes. However, combination of surgery and radiation in early stages does not improve outcomes in terms of local control rates or survival but definitely increases the treatment-related toxicities. Hence, proper patient selection and single radical treatment are associated with excellent outcome. This is possible in current era with the use of advancements in imaging modalities like MRI to identify adverse features like early parametrial involvement, depth of stromal invasion, significant uterine segment invasion and better selection for single modality treatment. Patients in whom need of postoperative adjuvant radiation is anticipated, chemoradiation should be preferred over surgery, as surgery followed by adjuvant radiotherapy is associated with significantly higher morbidity such as hydroureteronephrosis, intestinal obstruction and lower limb edema, compared to radical radiotherapy (28% vs. 12%) [14].

Nevertheless, in patients undergoing surgery, the decision regarding adjuvant therapy is a risk-adapted approach based on the final histopathology report and adverse features, including tumor size, vaginal cuff, parametrial dissection, number of nodes dissected, histopathological type, grade, vaginal and parametrial cut margins, depth of stromal infiltration, presence or absence of lymphovascular space invasion (LVSI) and nodal involvement. Patients planned for radical surgery, lymph node assessment intraoperatively and

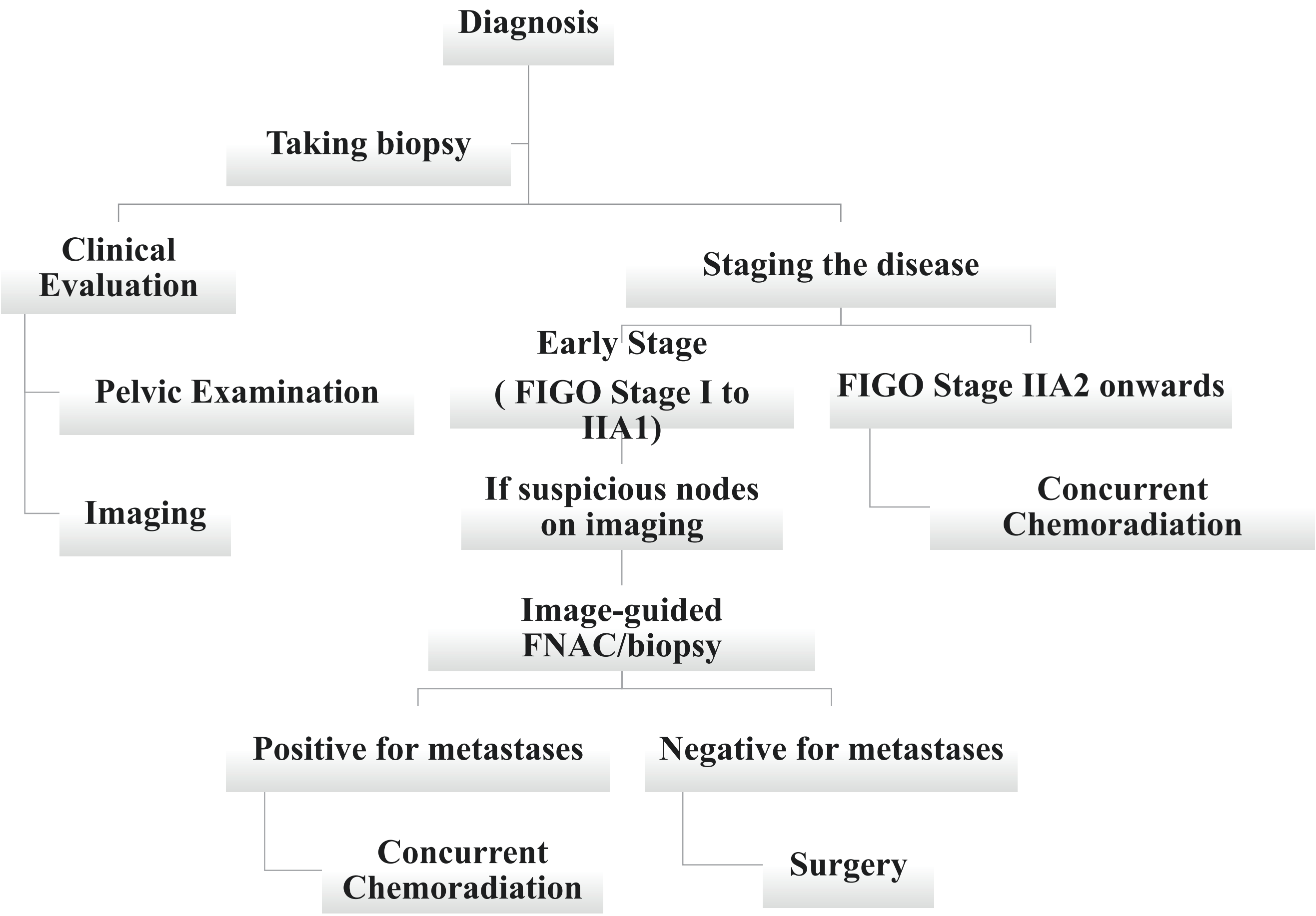

Diagnosis
Taking biopsy
Clinical Evaluation
Pelvic Examination
Imaging
Staging the disease
Early Stage (FIGO Stage I to IIA1)
FIGO Stage IIA2 onwards
If suspicious nodes on imaging
Concurrent Chemoradiation
Image-guided FNAC/biopsy
Positive for metastases
Negative for metastases
Concurrent Chemoradiation
Surgery

Fig. 2 Flowchart showing the principles of management of cervical cancer

frozen section evaluation if feasible and abandoning the primary surgery to offer chemoradiation may be useful.

Postsurgery, patients are deemed high risk if any one of the following features is present: lymph node metastases, positive surgical margins or positive parametrial extension. Adjuvant chemoradiation with external pelvic radiation therapy and concurrent weekly cisplatin chemotherapy are recommended [15]. In intermediate-risk patients as defined by the Sedlis criteria, in the absence of the high-risk features mentioned above and the presence of any two factors on final histopathology, namely, deep cervical stromal invasion, presence of LVSI or tumor size >4 cm, adjuvant pelvic radiation alone is recommended [16]. Low-risk patients are defined as having an absence of both high- and intermediate-risk features and require no further adjuvant.

Adjuvant radiation is delivered as external beam radiation therapy (EBRT) (preferably with intensity-modulated radiation therapy [IMRT] to reduce small bowel and hematological toxicity) to the pelvis to a dose of 45–50 Gy. A brachytherapy boost to the vaginal cuff may be added in patients at a high risk of local recurrence—close/positive surgical margins, simple hysterectomy with inadequate vaginal cut margins, parametrial or vaginal involvement, extensive LVSI and large tumor size. Alternatively, patients can also be offered definitive chemoradiation.

Patients with advanced stages (FIGO IIB–IIIB and select IVA) treated with radical chemoradiation including brachytherapy. Patients with advanced disease and not suitable of radical chemoradiation or metastatic disease are treated with palliative chemotherapy or radiation or both. In these patients it is important to incorporate palliative care early in the management to alleviate symptoms and improve QOL. The outcome of patients with relapse after definitive surgery with/without adjuvant therapy or chemoradiation is dismal. Salvage surgery for pelvic recurrences or chemoradiation for limited recurrences postsurgery is useful in only select group of patients and requires careful multidisciplinary discussion. Targeted therapy, especially with bevacizumab, has shown promising results with a median overall survival benefit of 4 months.

7 Surgical Management

The spectrum of surgery varies from radical trachelectomy to radical hysterectomy depending on stage and fertility desires of the patient. Early stage cervical cancers refer to cancers from FIGO stage I to stage IIA. The modalities of surgery and concurrent chemoradiation are equally effective in treatment of early stage disease. In small volume disease (size </=2 cm) and especially young sexually active females, surgery is advantageous. The advantages mainly include preservation of ovarian function and avoidance of radiation toxicities mainly vaginal stenosis. Although controversies exist in the management of bulky tumors (size >4 cm), surgery is still a viable option but should be done at a high-volume center with required expertise. Radical hysterectomy can be approached via open, laparoscopic or robotic surgery. However, recent evidence doesn't support the use of minimally invasive approach for radical hysterectomy [17–19]. At our institute, we proceed with bilateral pelvic lymphadenectomy at start and sending the nodes for frozen section. If the nodes are involved, procedure is abandoned and the patient is referred for concurrent chemoradiation. This approach helps prevent dual added morbidity of surgery and radiation. Radical hysterectomy is traditionally classified as suggested by Piver–Rutledge classification. In 2008, Querleu–Morrow classification based on fixed anatomical landmarks has been proposed. This classification has gained acceptance as it is also applicable for minimally invasive approaches and fertility-conserving surgeries. Both the classifications have been enlisted below [20, 21]. Nerve-sparing radical hysterectomy is an approach that avoids damage to the hypogastric and pelvic splanchnic nerves [22]. This helps avoid bladder, rectal and sexual dysfunction. However, at present, there is no level I evidence to prove its oncological safety.

7.1 Piver–Rutledge Classification (1974)

- Type 1: Extrafascial hysterectomy; removal of all cervical tissue
- Type 2: Modified radical hysterectomy; removal of medial half of the cardinal and uterosacral ligaments; the uterine vessels are divided medially to the ureter at the point of crossing of ureter
- Type 3: Classical Wertheim–Meigs operation; wide radical resection of the parametrium and paravaginal tissues with ligation of uterine vessels at the origin; ureter dissected completely to bladder entry; uterosacral ligaments divided at sacral attachment; cardinal ligament is divided at pelvic side-wall
- Type 4: Ureter is divided from pubovesical ligament; superior vesical artery ligated and upper two third of the vagina excised
- Type 5: Exenteration/extended radical hysterectomy with possible bowel, bladder or ureteric excision

7.2 Querleu–Morrow Classification (2008)

Type A:

- Minimum resection of paracervix, which is similar to extrafascial hysterectomy. The paracervix is transected medial to the ureter but lateral to the cervix.

Type B:
Transection of the paracervix at the ureter

- Partial resection of the uterosacral and vesicouterine ligaments, transection of the paracervix at the level of the Wertheim's tunnel.
- Type B1: without removal of paracervical lymph nodes
- Type B2: additional removal of paracervical lymph nodes

Type C:
Transection of paracervix at the boundary with internal iliac vessels

- Transection of the uterosacral ligament at the sacrum and vesicouterine ligament at the bladder.
- Type C1: with nerve preservation
- Type C2: without preservation of nerves

Type D:

- Laterally extended resection/exenterative procedures

7.3 Fertility-Conserving Surgeries

Radical trachelectomy and excisional conization are the surgical modalities used as fertility conserving approach for management of cervical cancer. Excisional conization can be considered appropriate for FIGO stage IA1 tumors without LVSI. The tissue is sent for frozen section and negative margins are to be confirmed. For tumors including FIGO stage IA1 with LVSI, IA2 and IB1 with preferred tumor size <2 cm, trachelectomy is the procedure of choice. It is to be emphasized that fertility-conserving approaches are not standard of care; these are deviations proven oncologically safe when the fertility desires of the patient are to be respected. Trachelectomy can be approached by either of vaginal, abdominal, laparoscopic or robotic route. Bilateral pelvic lymphadenectomy is done at the start of procedure, and the nodal tissue is sent for frozen section. It is proceeded once the report is negative for metastases. The criteria for selection of the patients who can be offered a fertility-conserving approach are listed below.

Criteria for fertility-conserving approach:

1. Strong desire for fertility preservation
2. Histopathology report of squamous carcinoma or adenocarcinoma
3. FIGO stage </=IB1 with preferable tumor size <2 cm
4. No evidence of nodal or distant metastases
5. Strong will for follow-up

8 Radiation and Medical Management

Patients with cervical cancer who are offered curative radio (chemo) therapy should always receive a combination of EBRT and brachytherapy (BT) with or with radiosensitizing platin-based chemotherapy [23].

8.1 External Beam Radiation Therapy (EBRT)

The main principle of EBRT for cervical cancer is to treat the primary tumor at cervix, gross nodal disease and the surrounding tissues with potential areas of spread (cervix uterus, parametria, upper vagina and ovaries—only in case of adenocarcinoma histology) and the draining regional pelvic lymph nodes (obturator, internal, external and common iliac, presacral). Typically, a dose of 45–50 Gy in 25 to 28 fractions with 5 fractions per week for 5 weeks is given to achieve optimal shrinkage of primary tumor to make it amenable for brachytherapy and to eradicate the microscopic disease in the other tissues. Patients suitable for concomitant chemoradiation will also receive weekly chemotherapy (detailed in next section). In case of pelvic lymph node involvement, EBRT may include the para-aortic region up to the renal vessels (45 Gy). In case of para-aortic lymph node involvement, EBRT volume includes the para-aortic region. Patients with gross nodal disease may be considered for additional doses as sequential or simultaneous radiation boost techniques.

Conventional/conformal pelvic box field (anterior–posterior and bilateral portals) techniques should be the minimum standards of EBRT as shown in Fig. 3. Newer radiation delivery techniques like IMRT, VMAT, etc. may also be used alternatively in experienced centers only. IGRT along with newer radiation techniques is highly recommended.

Typically, EBRT is delivered with the patient lying in the supine position with arms overhead/over the chest to keep them away from the radiation beam. A knee rest is placed below the knees to straighten the spine and fix the pelvis.

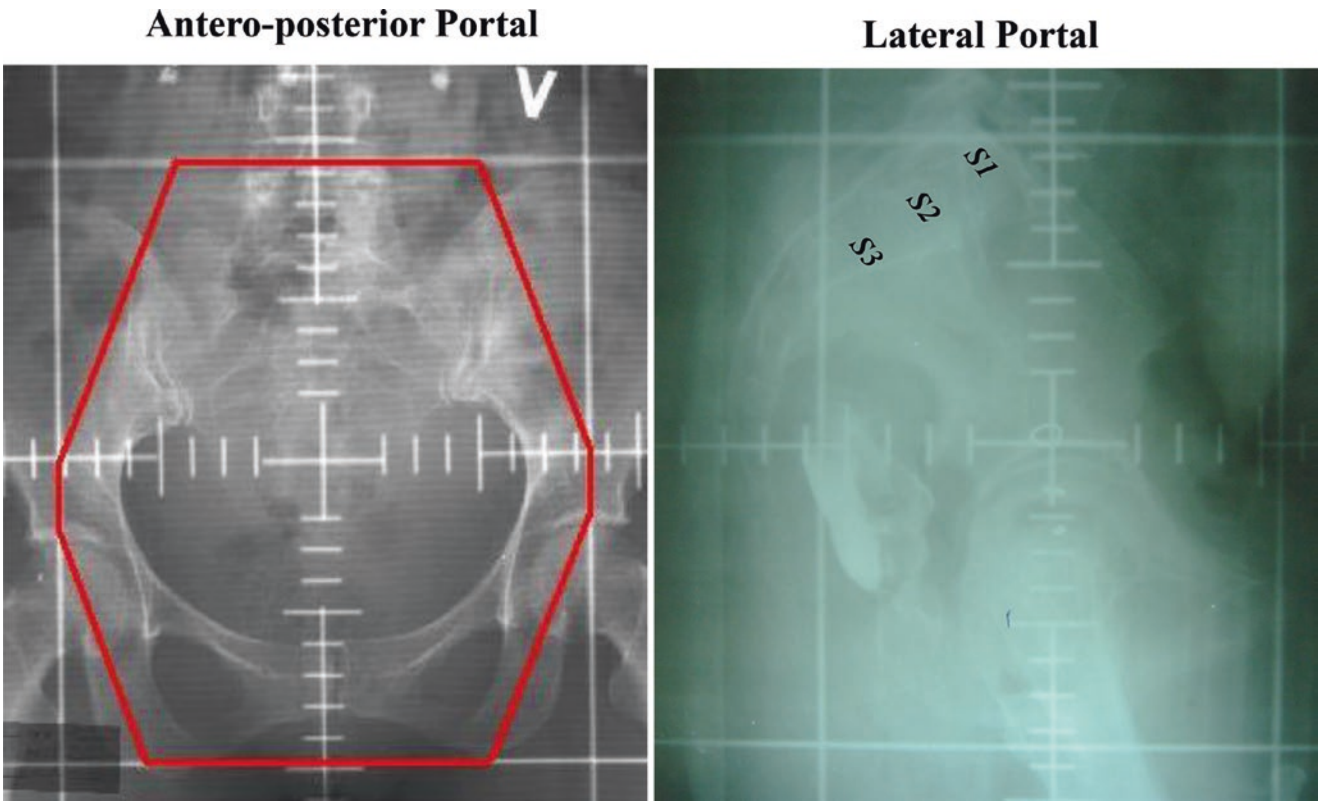
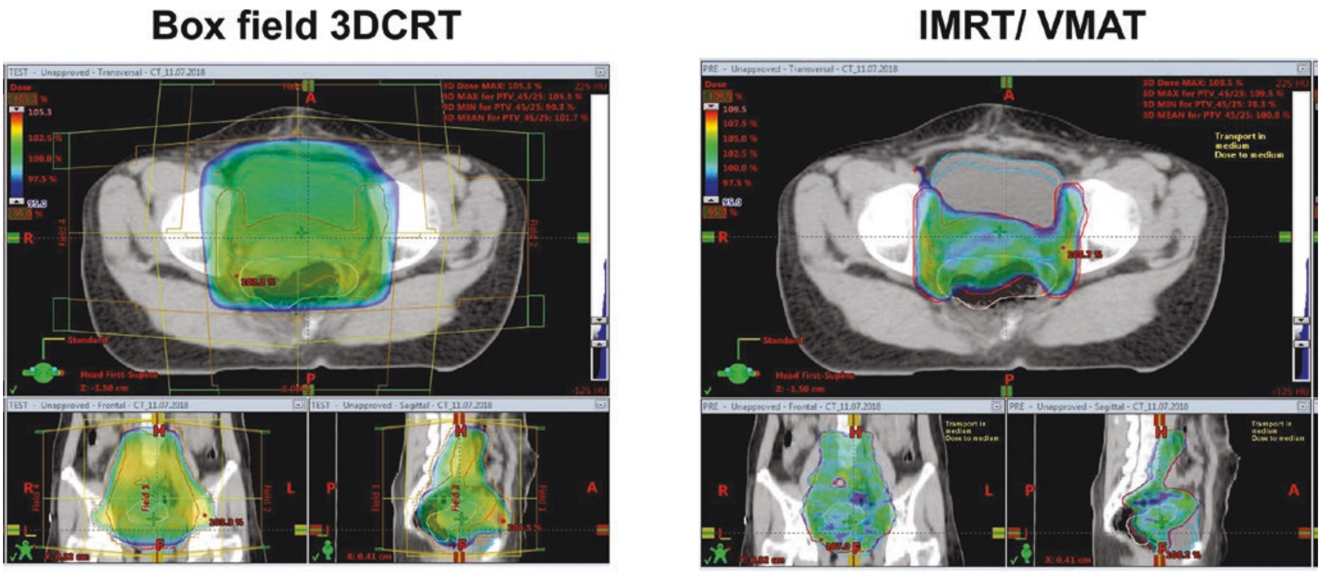


Fig. 3 Conventional EBRT techniques for cervical cancer external beam radiation therapy—two field or four field box techniques

Patients are treated with a comfortably full bladder using a bladder-filling protocol so that the small bowel is displaced out of the pelvic region as much as possible and to ensure reproducibility during the entire treatment. In conventional treatment planning, the radiation field borders are fixed corresponding to the bony landmarks of the patients, as seen on the simulator X-ray. A box field technique is usually used for the pelvis (see Fig. 3), where four radiation beams—anteroposterior, posteroanterior and two lateral beams—are used for treatment delivery. The superior border of the AP-PA fields is placed at the L4–L5 interspace to adequately cover the common iliac nodes, inferior border is placed 2 cm below the gross tumor in the vagina, which is marked with a radio-opaque marker during simulation. The lateral borders are placed 1.5–2 cm beyond the widest part of the pelvic brim. The superio-inferior borders of the lateral fields are same as those of the AP-PA fields, the anterior border is placed at the anterior edge of the pubic symphysis, and the posterior border at the junction of S2–S3 vertebrae. The three-dimensional conformal radiation (3D CRT) involves the use of MLCs (multileaf collimators) for shaping the radiation fields to the target volume. The advantage of CT images is the identification of the metastatic lymph nodes and adaptation of the target volumes accordingly for, for example, the lower para-aortic nodal region. Intensity-modulated radiation therapy (IMRT) and volumetric arc therapy (VMAT) are newer technologies for radiation delivery and are useful to minimize the doses to normal structures without compromise in the doses to the target. Figure 4 shows the isodose color wash comparison of 3D CRT versus IMRT for cervical cancer. These delivery techniques have been utilized in the treatment of cervical cancer and are particularly useful in the postoperative setting as the small bowel falls into the pelvis and is within the radiation portal in hysterectomized patients. These newer techniques have shown significant reduction in high-dose regions to neighboring structures dosimetrically; however, there is a lack of robust clinical evidence [24]. The use of newer radiation delivery techniques in definitive settings (intact cervix) is challenging due to organ motion (cervix, uterus and bladder/rectal volume reproducibility) and tumor regression during the course of treatment which introduces lot of uncertainties in daily treatment. To minimize the uncertainties, image guidance (IGRT) during radiation has been utilized and protocol needs to be institutionalized [24].

Nevertheless, use of newer RT techniques has been utilized for the following:

- *Prophylactic extended field radiation*: With increasing stage risk of para-aortic lymph nodes, involvement increases and would benefit with prophylactic treatment. Conventional treatments with 2D have been long criticized for increased bone marrow and bowel toxicity. But with IMRT, the doses of 50 Gy can be safely delivered to these regions [25, 26].
- *Treatment of para-aortic nodal region and pelvic/para-aortic nodal boost:* These regions may include pelvic or para-aortic lymph nodes. Patients with significant nodal burden in the low para-aortic or up to renal hilum have been treated with newer RT techniques with dose escalation up to 60–65 Gy for better control rates with acceptable toxicities [25, 26].



- High doses to OARs is significantly lower without compromising high doses to the target

Fig. 4 Newer conformal EBRT techniques. Three-dimensional conformal radiation (3D CRT) versus intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT)

- *Stereotactic radiotherapy and oligometastases*: The incidence of oligometastases (OLM) in cervical cancer accounts less than 10% and could be synchronous or metachronous. In case of synchronous OLM with primary disease, the outcomes of lymph nodal involvement beyond the regional lymphatics (mediastinal and left supraclavicular) are better as compared to visceral metastases [27]. In patients with metachronous OLM, the outcome is favorable provided there is no local disease. The mainstay of treatment is systemic therapy, with doublet chemotherapy; the addition of bevacizumab has shown modest improvement in overall survival in a recent study. In the recent past, high-dose radiation (in the form of stereotactic body radiotherapy (SBRT) and or brachytherapy to the primary site) with or without chemotherapy has been explored with encouraging results. In a multi-institutional analysis of SBRT in the above group of patients, the authors reported 3-year progression-free survival of 33% and median overall survival of 32 months, which is much higher than the use of systemic chemotherapy alone, which is less than a year [28].

8.2 Brachytherapy (BT)

BT is usually planned toward the end of EBRT typically fifth week onward and plays a very important role in obtaining high cure rates with minimum complications. Typically, BT delivers very high doses of radiation to the residual primary tumor and adjacent high-risk areas with optimal sparing of neighboring organs/tissues namely bladder, rectum, sigmoid and/or bowel. The principles of BT include, BT application, imaging, planning and treatment. The brachytherapy application is done under anesthesia/sedation—bi-digital pelvic examination is mandatory to assess residual disease, identification and sounding of uterine canal (assisted by ultrasonography, if available), insertion of BT applicator assembly which consists of a straight tube in uterine canal called tandem, and a vaginal component placed in the lateral fornices, either in the form of a ring or two ovoids, which are usually perpendicular to axis of tandem, followed by vaginal packing to stabilize the applicator assembly. Imaging (orthogonal X-rays or CT/MRI) of the pelvic region is done. Figure 3 illustrates different types of brachytherapy applicators currently available for cervical cancer brachytherapy. Treatment planning is performed by medical physicist. The steps involved in planning include identification and reconstruction of applicator channels, source loading, defining patient/applicator-related points (point "A," ICRU bladder and rectal points) dosimetry, plan evaluation and finalization. BT treatment delivery is done using BT machine (commonly HDR BT).The radioactive source (Ir192/Co60) is introduced into the applicator via a remote after-loading machine, thus causing minimal exposure to the radiation personnel. BT is usually delivered in several fractions (3–4 fractions) with high-dose rate (HDR) or 1 to 2 fractions of pulse dose rate (PDR) [29].

8.3 Recent Advances in Cervical Brachytherapy

Conventional BT planning and treatment has been orthogonal radiography with Point "A" and ICRU 38 recommendations. The major limitation of the conventional imaging modalities is applicator and point based and there is a lack of information on the tumor volumes and organs at risk (OAR). In the last two decades, significant technological advances have resulted in use of newer imaging modalities like MR, CT, CT/MR-compatible applicators, better planning algorithms and treatment delivery. This has resulted in use of imaging techniques for three-dimensional data acquisition, defining residual disease, target, and various organs and optimize treatment planning Among the imaging modalities, MR imaging is becoming increasingly popular for diagnosis and treatment planning for EBRT and brachytherapy and has been established as gold standard for management of cervical cancer especially in developed world [30, 31].

MR image-guided adaptive BT (IGABT) processes has been established by GEC-ESTRO and the latest ICRU 89 report describes in detail [30–32]. The highlights include use of repetitive cross-sectional imaging including at BT with applicators in place, definition of various targets related to residual disease (GTV, HR-CTV, IR-CTV), planning and plan optimization to the target and prescribing/reporting of dose volume parameters in relation to the target and organs as detailed in Fig. 5. The outcome published from many mono-institutional series and preliminary results from multicentric retrospective and prospective studies indicate excellent local control rates of 95%–100% at 3/5 years in limited/favorable (IB/IIB) and 85–90% in large/poor response (IIB/III/IV) groups with acceptable treatment-related morbidity rates so far. Compared to the historical conventional BT series there is relative reduction in pelvic recurrence and reduction in major morbidity [33, 34].

Other imaging modalities like ultrasonography (US), CT scan or combinations as alternatives for IGABT are also being explored now. The CT has also been compared with MRI in few small dosimetric studies and need validation in larger clinical studies [35, 36].

8.4 Combined EBRT and BT Doses

With combination of EBRT and BT radiation, the overall aim is to deliver a tumoricidal doses of at least 75–80 Gy equivalent doses (EQD2) to point "A" or at least 85 Gy to the resid-

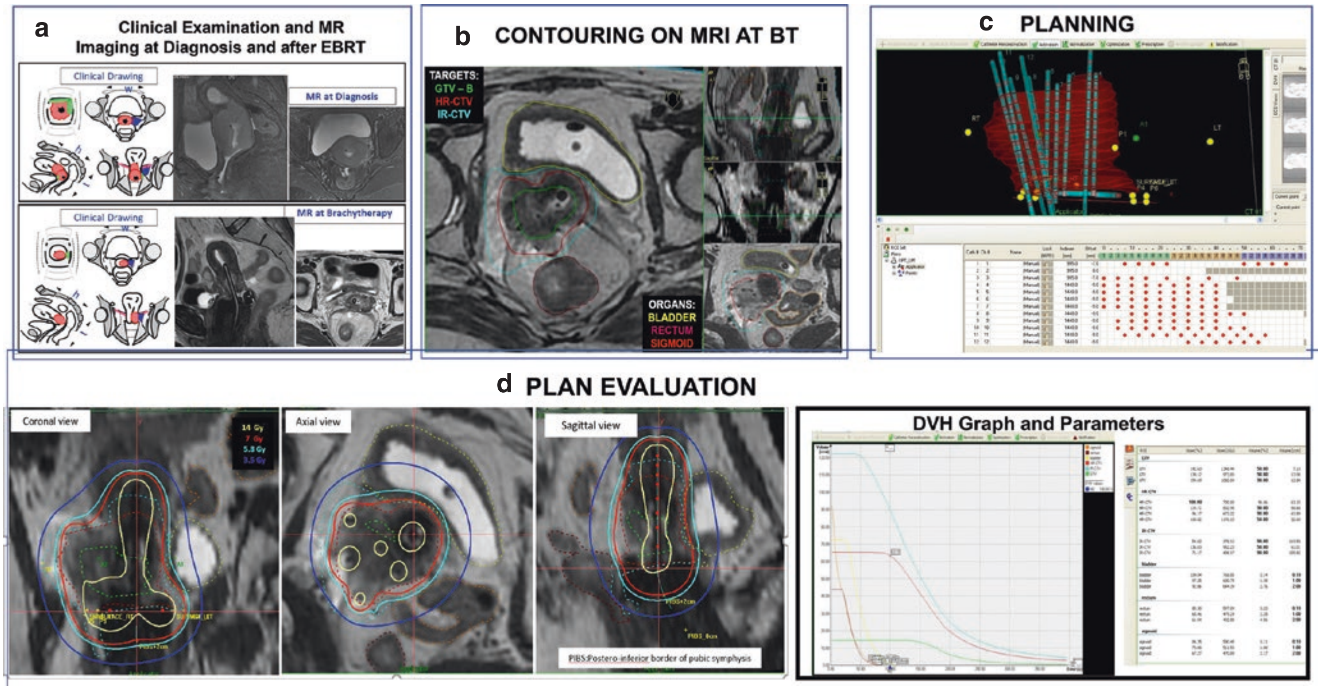

a
Clinical Examination and MR Imaging at Diagnosis and after EBRT
Clinical Drawing
MR at Diagnosis
Clinical Drawing
MR at Brachytherapy
b
CONTOURING ON MRI AT BT
TARGETS:
GTV – B
HR-CTV
IR-CTV
ORGANS:
BLADDER
RECTUM
SIGMOID
c
PLANNING
d
PLAN EVALUATION
Coronal view
14 Gy
7 Gy
5.5 Gy
3.5 Gy
Axial view
Sagittal view
PIBS:Postero-inferior border of pubic symphysis
DVH Graph and Parameters

Fig. 5 Principles of MR image-guided brachytherapy (MR IGABT) for cervical cancer

ual primary disease after EBRT for all stages. The overall treatment time (OTT) for completion of the entire course of radiation therapy EBRT and BT should be within 7–8 weeks, with delay beyond this time frame resulting in compromise in local control rates [37].

8.5 Side Effects Related to Radiation Therapy

Acute toxicities during pelvic radiotherapy are very common. Most patients experience mild to moderate fatigue, diarrhea, increased frequency & dysuria. The symptoms are more pronounced in 4th–fifth weeks of EBRT. Supportive and symptomatic treatment in the form of antidiarrheal medications, alkylating agents and hydration provide adequate relief of symptoms. The acute side effects are more pronounced when combined with weekly radiosensitizing chemotherapy or extended filed radiation therapy. In addition, hematological and renal toxicities are seen in patients receiving concurrent chemotherapy especially with Cisplatin/carboplatin [38].

The late toxicities after combined EBRT and BT commonly seen are rectal, bladder, small bowel and vagina. The clinical spectrum of late effects depend on the estimated radiation doses to the organs, type of treatment modalities, follow-up duration and disease-free interval. Typically, grade III/IV late sequelae (toxicities requiring hospital admission or intervention) are reported between 18 and 36 months posttreatment period but can appear as early as 6–9 months also and range between 5% and 15% and are seen any time after 6 months posttreatment period commonly between 18 and 36 months.

The clinical spectrum of late rectal toxicities include, tenesmus, telangiectasia, profuse painless bleeding, ulceration, rectovaginal fistula and strictures in 5–8%; late bladder toxicities, in the form of continuous painless hematuria, necrosis and rarely vesicovaginal or urethra-vaginal fistula (4%–8%); and small bowel late toxicities, including chronic enteritis, subacute intestinal obstruction, perforation and strictures in 3–12%, have been reported. The principles of management of late radiation toxicities are conservative except in severe life threating situations. Sucralfate enema, steroid enema, argon plasma coagulation (APC), laser therapy, or formalin applied to affected mucosa, diversion colostomy for rectal toxicities, hyperbaric oxygen therapy for hematuria and conservative or surgical intervention for small bowel late toxicities have been tried.

Lastly, telangiectasia, atrophy and fibrosis of the vagina, resulting in significant vaginal shortening, especially in elderly, postmenopausal women and those with extensive tumors treated with high doses of radiation is seen. These, to a large extent, can be prevented by early intervention in the form of vaginal dilatation exercises and counseling for regular sexual activity.

8.6 Concurrent Chemoradiation

The rationale of using concurrent chemotherapy with radiation is to increase the local tumor control by enhancing radiation action using radiosensitizing effects of various chemotherapeutic drugs, which would translate into better survival. Cisplatin is the most effective chemotherapeutic drug in treating cervical cancer. It acts synergistically with radiation by binding to DNA and causing inter- and intra-strand cross-links; it prevents repair of DNA damage caused by radiation. Cisplatin is nephrotoxic, ototoxic and myelosuppressive. It must be administered with adequate hydration and periodic monitoring of blood counts, renal function and audiometry. For cervical cancer, cisplatin is administered weekly, at 40 mg/m^2, and ideally an hour before a radiation fraction. Dose modification is required in patients with impaired renal function. Multiple randomized phase III trials comparing concurrent chemotherapy with radiation to RT alone, and their meta-analysis have shown an absolute benefit in disease-free and overall, with chemoradiotherapy in patients with stage IB2 to IVA disease as well as high-risk patients after hysterectomy [39]. A recent trial from our country exclusively included patients with III B cervical cancer, demonstrated an absolute benefit in DFS of 8.5% and OS of 6% at 5 years with addition of chemotherapy [40]. This reiterates the benefit of chemotherapy in our patient population, a larger number of who present with more advanced disease and were earlier thought to be poor candidates for concurrent chemotherapy due to poor nutritional/performance parameters as a result of poor socioeconomic status. Thus, concomitant chemoradiotherapy is the standard of care for locally advanced cervical cancer, with cisplatin being the chemotherapeutic agent of choice.

8.7 Neoadjuvant Chemotherapy in Cervical Cancers

8.7.1 Neoadjuvant Chemotherapy and Surgery

Several randomized trials and a meta-analysis of neoadjuvant chemotherapy followed by surgery versus surgery have been reported in FIGO Stage IB–IIB and have not shown any improvement in clinical outcomes. However, in the recent past, two large randomized trials (NCT00039338, NCT00193739) have been reported: one from Tata Memorial Hospital has reported inferior disease outcomes, while the final results of EORTC study are awaited [41].

8.7.2 Neoadjuvant and Adjuvant Chemotherapy and Radiation Therapy/Chemoradiation

In locally advanced disease, meta-analyses evaluating several randomized trials of neoadjuvant chemotherapy followed by radiation therapy have also reported negative results for outcome as compared to radiation alone [42]. However, subset analyses have shown that dose-dense and dose-intense chemotherapy had some benefit. Moreover, comparison with concurrent chemoradiation is lacking in the literature and is a subject of clinical research. A large randomized multicentric trial is ongoing (INTERLACE study—NCT01566240) to test improvement in survival after dose-dense paclitaxel-carboplatin neoadjuvant chemotherapy prior to radiochemotherapy versus radiochemotherapy.

Other aggressive treatment approach after completion of radical chemoradiation is to treat occult spread especially in locally advanced cervical cancers. One large randomized trial evaluated the role of thrice weekly cisplatin (50 mg/m^2) and gemcitabine for two cycles after chemoradiation reported significant acute grade III/IV hematological toxicities and moderate improvement in survivals, but this is practically difficult to implement in clinical practice out-of-trial settings, especially in LMIC/LICs. There are ongoing randomized trials (NCT00980954, NCT00141608), evaluating the role of paclitaxel—cisplatin or paclitaxel—carboplatin (Outback trial) adjuvant chemotherapy after chemoradiation.

8.8 Systemic Therapy

Patients with metastatic disease at presentation and recurrent disseminated disease are not curable and the intent of treatment is palliation of symptoms and prolongation of survival. Palliative chemotherapy especially combination chemotherapy regimens have generally been shown to improve response rates (RR) and progression-free survival (PFS) but not overall survival (OS) compared to single-agent cisplatin [43]. Most commonly used regimen is paclitaxel and either cisplatin or carboplatin [44, 45]. Carboplatin is preferred over cisplatin due to ease administration and better tolerability in terms of emesis, renal toxicities, ototoxicities, etc. Although there is no randomized phase III evidence for carboplatin, but there are several retrospective analyses and prospective nonrandomized studies that indicate equivalent efficacy. Carboplatin is substituted for cisplatin in many regimens by most clinicians. Another regimen that has been tested in a randomized phase III trial is topotecan plus cisplatin that was shown to be superior to single agent cisplatin with respect to RR, PFS and OS [46]. However, it is not usually preferred regimen due to its unfavorable toxicity profile, including myelosuppression and gastrointestinal toxicity. A recent phase III trial compared 4 platinum doublets (cisplatin + either of the following: paclitaxel, topotecan, gemcitabine and topotecan). There were no statistically significant differences in OS but there was a trend to superiority of cisplatin-paclitaxel in RR, PFS and OS [47]. Other agents uncommonly used as second line palliative chemotherapy include vinorelbine, irinotecan, ifosfamide and 5-FU. In patients in whom peripheral neuropathy is a concern, gemcitabine-platinum is an acceptable alternative. Carboplatin is substituted for cisplatin in many regimens by most clinicians. Generally, four to six cycles of chemotherapy are used.

In the recent past, several targeted therapies including bevacizumab have been tried. Use of bevacizumab in combination with other chemotherapy regimens has recently shown an absolute improvement in median overall survival by 4 months in patients with recurrent, metastatic cervical cancer [48].

8.9 Palliative Treatment

All patients should be registered for integrated palliative care approach, early in the course of metastatic and recurrent disease. Counseling and symptom control are some of the important components. Apart from general medications for symptom control including analgesics (especially opioids), prokinetics, effective palliation of symptoms due to disease (local, bone & brain metastasis, enlarged nodal disease) can be tackled with local radiation therapy. Palliative radiotherapy regimens typically range from 1 to 10 treatments delivered over 1–2 weeks. Palliative chemotherapy is generally used because there is some evidence that it may palliate symptoms and/or prolong survival in this setting**.** However, patients with poor performance status are not candidates for palliative chemotherapy, in general. Lastly, patients also benefit for best supportive care.

9 Cervical Cancer and Pregnancy

Every patient diagnosed with cervical cancer in pregnancy should be reviewed in multidisciplinary tumor board clinic including an Obstetrician and preferably managed at a tertiary cancer care center. With the wide-spectrum of treatment modalities available, management of cervical cancer and pregnancy should be individualized based on patients understanding and desire to maintain the pregnancy, gestational age, pregnancy outcome, tumor stage and oncological safety of pregnant women and the fetus. The work-up evaluation includes clinical examination, histological confirmation (cone biopsy should be avoided), ultrasonography of abdomen and pelvis to evaluate primary and gross nodal disease and kidney status and if required MRI abdomen and pelvis. CT or PET-CT imaging should be avoided.

In general, based on the patient’s performance status, comorbidities, stage and gestational age, appropriate management, including proper counseling on risk and benefits, prtcome, and treatment are planned.

In patients with noninvasive disease, all attempts should be made to preserve pregnancy (if desired) and conservative LEEP, conization with cerclage, diathermy or delay in definitive treatment options should be discussed [49–51].

In patients with invasive disease, radical surgery, including removal of the tumor (conization, simple or radical trachelectomy) and LN staging according to the stage of the disease with the intent to preserve the pregnancy or radical surgery/primary chemoradiation as recommended for the stage of the disease without preservation of the pregnancy, with or without previous pregnancy termination, can be offered.

Attempts should be made to delay the oncological treatment until fetal viability (at least 24 weeks) and/or >32 weeks followed by cesarean delivery and cancer stage-specific treatment. Spontaneous delivery should be avoided. Neoadjuvant chemotherapy until fetal viability has been a successful treatment without major risks. Neoadjuvant chemotherapy can be initiated as early as 14 weeks gestation period. If the patient does not wish to preserve pregnancy, medical termination followed by stage-based appropriate treatment similar to that for the nonpregnant patient should be offered.

10 Cervical Cancer and HIV

In patients with retroviral positive, there is higher incidence of in situ and invasive cervical cancer and usually diagnosed at an earlier age as compared to negative patients [52]. Antiretroviral therapy (ARV) should be integrated in the treatment because it reduces AIDS-related causes of death by 75%. The medical management of retroviral positive and AIDS patients diagnosed with cervical cancer should follow the general guidelines for the treatment of cervical cancer.

Treatment offered depends on the stage of disease and general performance status, irrespective of their retroviral status. The radiation therapy details remain similar to other patients. These patients are at higher risk of toxicities (acute and late) due to low immune status and hence need more rigorous monitoring [52].The indication for chemotherapy is tailored to the performance status and immune status of the patient. Chemotherapy is avoided if the CD4 count is below 200 cells/mm^3. Patients receiving chemotherapy are at higher risk for myelosuppression; hence, careful monitoring is required.

11 Management of Other Histologies

11.1 Adenocarcinomas, Adenosquamous, Adenoid Cystic Carcinomas

These histologies, although not common, are biologically aggressive and associated with poor prognosis as compared to classical squamous carcinoma histology. Hence, aggressive treatment protocols are attempted to achieve optimum outcome for, for example, neoadjuvant chemotherapy, radical surgeries, concomitant chemoradiation and adjuvant chemotherapy.

11.2 Neuroendocrine Small Cell Carcinomas

Patients with small cell carcinomas of cervical cancer are approached based on the experience from the lung variant small cell carcinoma, utilizing cisplatin etoposide-based chemotherapy and concomitant chemoradiotherapy with or without prophylactic cranial radiation. The outcome is unfavorable, with 3-year survival less than 30%.

12 Management of Recurrent Disease

Based on various factors like sites, single or multiple, performance status, comorbidities, etc. an upfront decision on curative versus palliative treatment is vital. Treatment of recurrent disease with curative intent requires super-centralization, involvement of a multidisciplinary team including gynecologic oncologist, radiation oncologist, radiologist, pathologist, medical oncologist, urologist, plastic surgeons, etc. and tumor board discussions.

Diagnostic work-up to identify exact patterns of relapse, locoregional, distant and combination of relapses and histological confirmation of recurrence should be performed.

Patients with multiple nodal, distant metastasis or multiple locoregional or fixed pelvic wall are usually considered for palliative treatment only, while others are candidates for curative salvage treatments after proper counseling about the risks, side effects, consequences and QOL.

12.1 Local Recurrence After Primary Surgery

Central or lateral pelvic recurrences after surgery are treated by chemoradiation and BT or pelvic exenteration in selected patients only. Chemoradiation or radiation therapy alone with interstitial BT results in optimal outcome with reasonable acceptable toxicities [53]. Pelvic exenteration may be an alternative (particularly if a fistula is present) in selected patients without pelvic sidewall involvement. Alternately, whole pelvic radiochemotherapy followed by a stereotactic ablative boost or stereotactic ablative radiation with newer radiation techniques including photon or particle beam are emerging and should be encouraged to participate in clinical research.

12.2 Local Recurrence After Primary Radiotherapy

Selected patients with isolated central recurrences should be considered for pelvic exenteration. The relative indications include patients with resectable central recurrences that involve the bladder and/or rectum and resectable pelvic sidewalls without evidence of intraperitoneal or extrapelvic spread. However, majority of patients are not suitable for surgery due to poor performance status, low albumin and high morbidity rates.

Role of chemotherapy before surgery in the management of recurrent disease is currently unclear. Not more than two to four courses of combination chemotherapy should be given to avoid unnecessary long interval before definitive surgery or radiotherapy. Locoregional recurrences, which at diagnosis appear incurable should be reassessed for the possibility of radical treatment if major response to chemotherapy (2–4 cycles) is obtained. The role of biological target agents is currently unclear. There is currently limited evidence to support the use of adjuvant chemotherapy following radical surgical treatment of the recurrence. However, adjuvant chemotherapy can be considered in cases carrying a high risk of recurrence such as positive margins, positive LN, or LVSI-positive tumors. Suitable candidates for adjuvant chemotherapy are patients who recover well within 2 months after primary treatment for recurrence.

Other spectrum of recurrence include, triad of unilateral leg edema, sciatic pain and ureteral obstruction almost always indicates unresectable disease on the pelvic sidewall, and are usually offered palliative treatments only.

13 Prognosis and Outcome

The most important prognostic factor for cervical cancer is staging including nodal disease. In patients with node-negative disease, outcome depends on local staging. Hence, clinical examination and imaging for local staging become vital. Similarly, in node-positive patients apart from local staging, imaging/surgical sampling to identify pathological regional nodal disease defines the outcome in cervical cancer.

In patients with early cervical cancer who undergo radical surgery, the surgicopathological factors related to resection status, histology type, grade, depth of stromal invasion, LVSI, tumor dimension, cut margins, positive parametrial and nodal disease are important tumor-related prognostic factors that also form the basis for risk-adapted treatment approach. Apart from these, nodal yield, number of nodes positivity, etc. also are important for disease outcome.

For locally advanced disease, apart from local and nodal staging, other tumor and treatment-related factors including, type of tumor (exophytic versus endophytic), presence of necrosis, uterine corpus invasion, hydronephrosis, unilateral or bilateral parametrial involvement, imaging biomarkers like PET uptake values, restricted diffusion on MR, response to chemoradiotherapy, residual disease at brachytherapy, radiation doses, compliance to completion of treatment (overall treatment time <8 weeks), adequate chemotherapy cycles and doses define the outcome of the patients.

Patient-related prognostic factors include age, smoking, anemia, high pretreatment leukocyte counts, presence of pelvic inflammatory disease (PID), previous pelvic surgeries, retroviral infection status and nutritional status also influence the treatment, compliance and disease outcome.

13.1 Disease Outcome

In early stage invasive cancers (FIGO I-IIA), the 5-year survival rates reported with various treatment modalities range between 88% and 95%. As described earlier, all attempts should be made to offer single-modality treatment to minimize the treatment-related late effects and improve the QOL. For locally advanced disease treated with radical intent, with radiation therapy alone, 5-year survival rates of 65%–75%, 35%–50% and 30% have been shown for FIGO IIB, IIIB and IVA, while contemporary series of chemoradiation have shown further improvement in 5-year survival by 7–10%.

13.2 Follow-Up

After completion of treatment and establishing complete response, all patients should be counseled for regular follow-up for early detection of recurrence, treatment-related complications, and rehabilitation, including change in lifestyles.

More than 80% of recurrences are seen within 2 years after the treatment; hence, follow-up should be more intense during this period—once every 3–4 months for the first 2 years followed by every 6 months for the next 3 years and annually subsequently. All patients should be evaluated by experienced team to identify early recurrences and treatment-related side effects. Follow-up evaluation should include patient history with elicitation of relevant symptoms and physical examination including a speculum examination and bimanual pelvic examination. Imaging and laboratory tests are not routinely advocated in asymptomatic patients [54]. Suspicious lesions should be biopsied. The vaginal vault cytology has low positive predictive value to detect recurrence in asymptomatic population especially postradiation and is therefore not routinely recommended. Patients should be encouraged and educated regarding regular use of vaginal dilators and sexual activity (if applicable) to avoid long-term vaginal toxicities.

Hormone replacement therapy should be offered, especially to the younger patients who are long-term survivors, as per the premature menopausal management guidelines. Combined estrogen–progesterone preparations are generally given to patients with uterus in situ, while estrogens are given to patients who have undergone hysterectomy.

Treatment Algorithms According to FIGO (2018) Staging—Cervical Cancer (Figs. 6, 7, 8, 9, 10, 11, 12, 13)

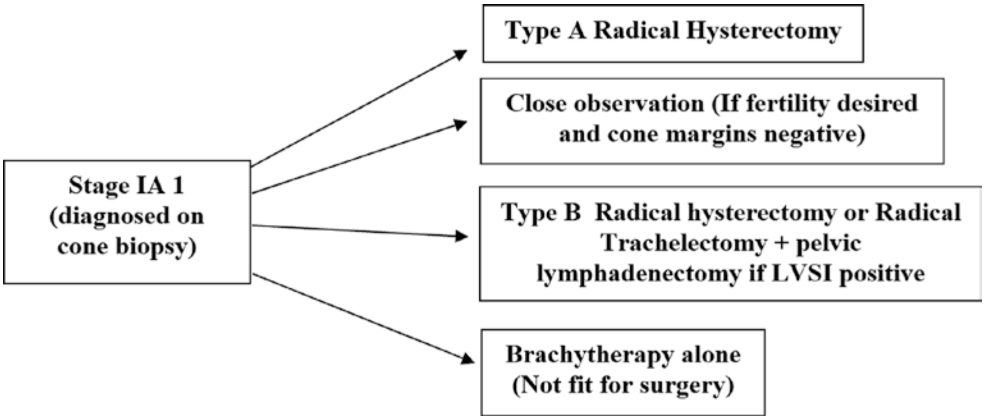

Stage IA 1
(diagnosed on
cone biopsy)
Type A Radical Hysterectomy
Close observation (If fertility desired
and cone margins negative)
Type B Radical hysterectomy or Radical
Trachelectomy + pelvic
lymphadenectomy if LVSI positive
Brachytherapy alone
(Not fit for surgery)

Fig. 6 FIGO (2018) stage IA1 treatment algorithm at TMC

Fig. 7 FIGO (2018) stage IA2 treatment algorithm at TMC

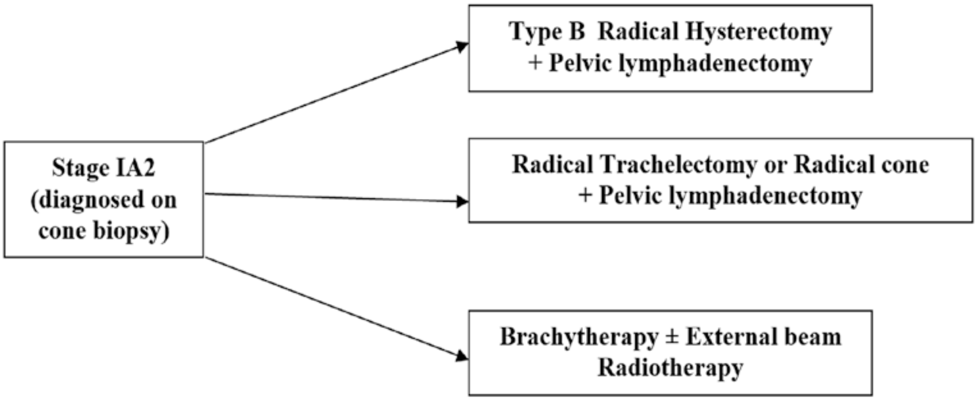

Stage IA2 (diagnosed on cone biopsy)
Type B Radical Hysterectomy + Pelvic lymphadenectomy
Radical Trachelectomy or Radical cone + Pelvic lymphadenectomy
Brachytherapy ± External beam Radiotherapy

Fig. 8 FIGO (2018) stage IB1–2 and IIA1 treatment algorithm at TMC

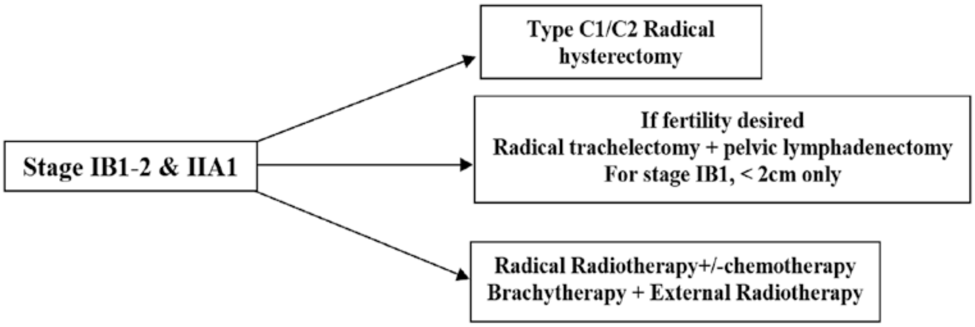

Stage IB1-2 & IIA1
Type C1/C2 Radical hysterectomy
If fertility desired
Radical trachelectomy + pelvic lymphadenectomy
For stage IB1, < 2cm only
Radical Radiotherapy+/-chemotherapy
Brachytherapy + External Radiotherapy

Fig. 9 FIGO (2018) postradical surgery adjuvant treatment algorithm at TMC

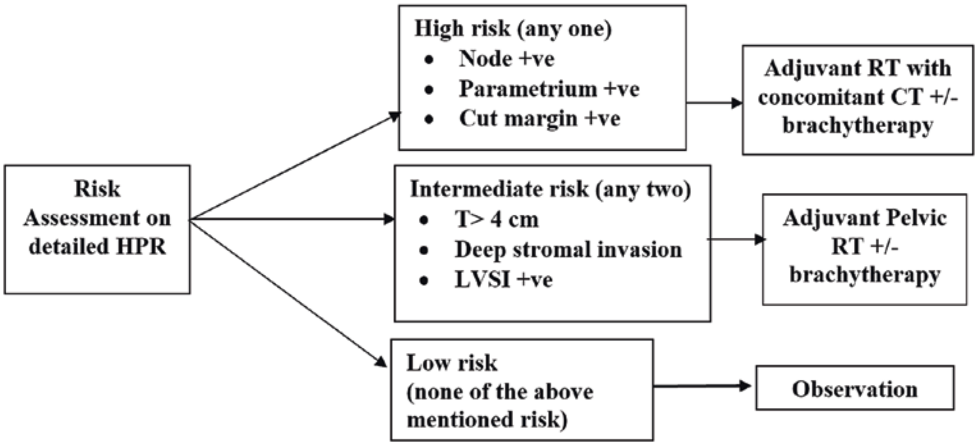
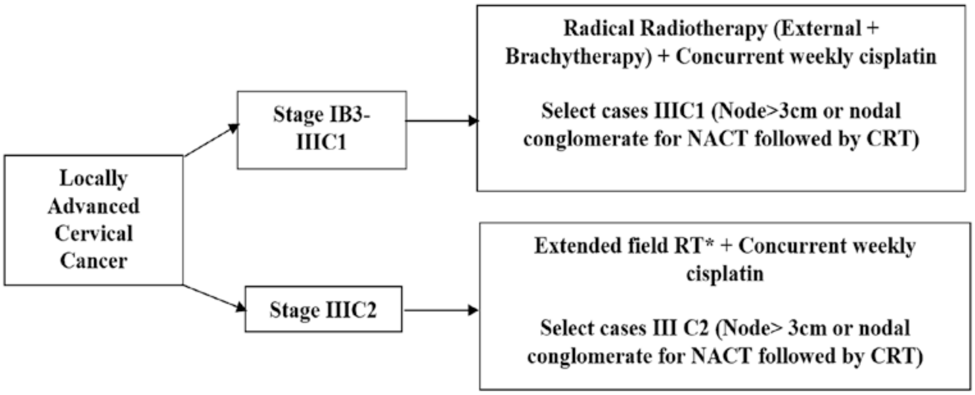

Risk Assessment on detailed HPR
High risk (any one)
Node +ve
Parametrium +ve
Cut margin +ve
Adjuvant RT with concomitant CT +/- brachytherapy
Intermediate risk (any two)
T> 4 cm
Deep stromal invasion
LVSI +ve
Adjuvant Pelvic RT +/- brachytherapy
Low risk (none of the above mentioned risk)
Observation

Fig. 10 FIGO (2018) stage IB3–IIIC2 treatment algorithm at TMC


Locally Advanced Cervical Cancer
Stage IB3-IIIC1
Radical Radiotherapy (External + Brachytherapy) + Concurrent weekly cisplatin
Select cases IIIC1 (Node>3cm or nodal conglomerate for NACT followed by CRT)
Stage IIIC2
Extended field RT* + Concurrent weekly cisplatin
Select cases III C2 (Node> 3cm or nodal conglomerate for NACT followed by CRT)

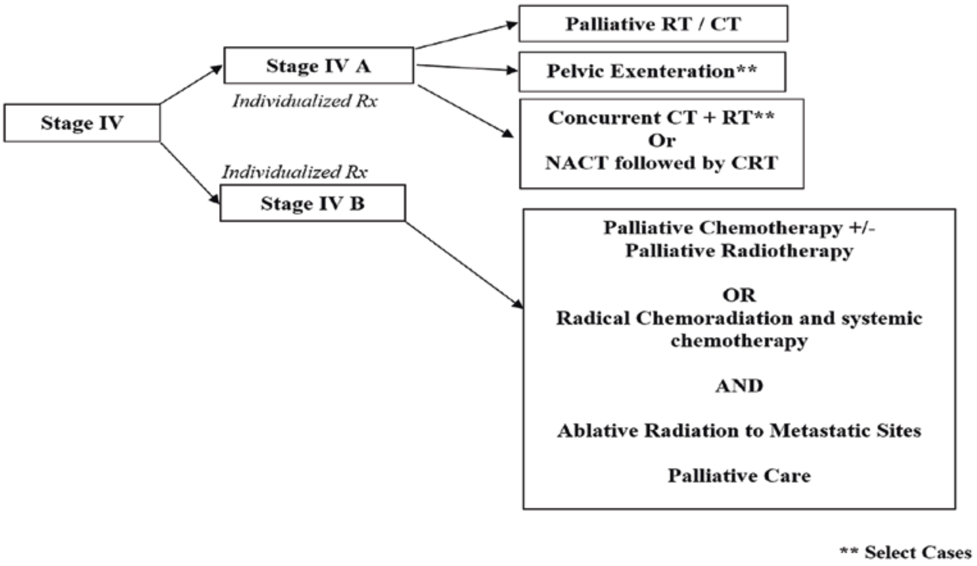

Stage IV
Stage IV A
Individualized Rx
Individualized Rx
Stage IV B
Palliative RT / CT
Pelvic Exenteration**
Concurrent CT + RT**
Or
NACT followed by CRT
Palliative Chemotherapy +/-
Palliative Radiotherapy
OR
Radical Chemoradiation and systemic chemotherapy
AND
Ablative Radiation to Metastatic Sites
Palliative Care
** Select Cases

Fig. 11 FIGO (2018) stage IV treatment algorithm at TMC

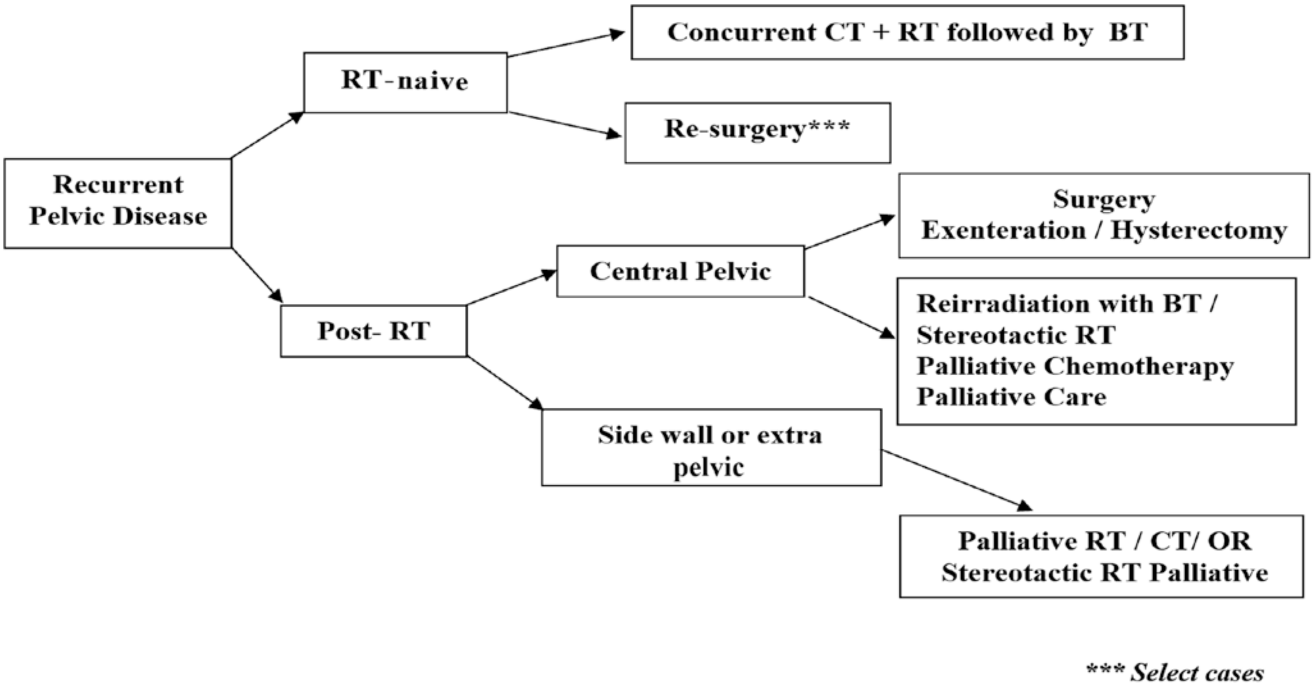

Recurrent Pelvic Disease
RT-naive
Post- RT
Concurrent CT + RT followed by BT
Re-surgery***
Central Pelvic
Side wall or extra pelvic
Surgery
Exenteration / Hysterectomy
Reirradiation with BT /
Stereotactic RT
Palliative Chemotherapy
Palliative Care
Palliative RT / CT/ OR
Stereotactic RT Palliative
*** Select cases

Fig. 12 FIGO (2018) posttreatment recurrent pelvic disease treatment algorithm at TMC

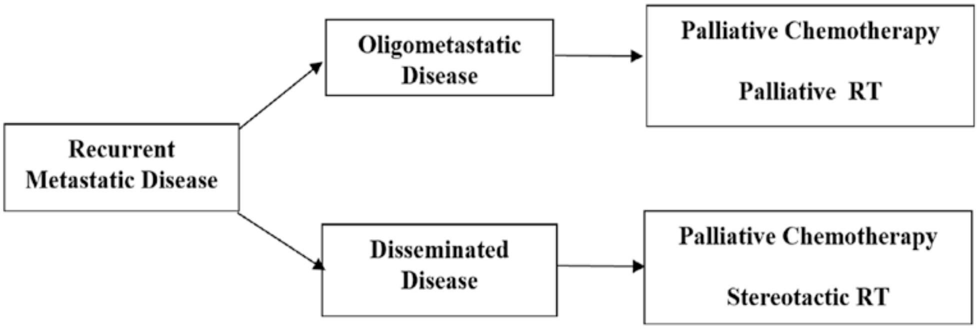

Recurrent Metastatic Disease
Oligometastatic Disease
Disseminated Disease
Palliative Chemotherapy
Palliative RT
Palliative Chemotherapy
Stereotactic RT

Fig. 13 FIGO (2018) posttreatment recurrent metastatic disease treatment algorithm at TMC

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Check for updates

Vulvar and Vaginal Cancers

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Arnab Bhattacharjee, and Jyoti Bajpai

Abbreviations

ASCCP	American Society for Colposcopy and Cervical Pathology
CAP	College of American Pathologists
DES	Diethylstilbestrol
DOI	Depth of invasion
dVIN	VIN of differentiated type
FNPV	False-negative predictive value
GOG	Gynecological Oncology Group
HPV	Human papilloma virus
HSIL	High-grade squamous intraepthelial lesion
IHC	Immunohistochemistry
IMRT	Intensity-modulated radiotherapy
ISGYP	International Society of Gynecologic Pathologists
ISSVD	International Society for the Study of Vulvovaginal Disease
LAST	Lower Anogenital Squamous Terminology
LS	Lichen sclerosus
LSIL	Low-grade squamous intraepithelial lesion
SEER	Surveillance Epidemiology and End Results
SLNB	Sentinel inguinal lymph node biopsy
uVIN	VIN of usual type
VAIN	Vaginal intraepithelial neoplasia
VIN	Vulvar intraepithelial neoplasia
VSCC	Vulvar squamous cell cancer

1 Introduction

The incidence of preinvasive vulval cancers has increased over the past 30 years, owing to increased awareness and detection of vulvar intraepithelial neoplasia and also their more effective treatment thus preventing the development of vulvar cancer. The incidence of vulvar squamous cell cancer (VSCC), on the other hand, has remained relatively unaltered. An analysis of 13,176 patients in the SEER (Surveillance Epidemiology and End Results) database between 1973 and 2000 found that VIN increased by 411%, while VSCC only increased by 20% [1]. Cancer registry in India, as in 2015, showed a heterogeneous incidence of vulvar carcinoma across the country. During the year 2003–2007, the crude rate was 0.2–0.5 per 100,000 women per year. A pooled incidence in different cities showed a rise in incidence between the age groups of 50 and 70 years [2]. Most vulval cancers occur in postmenopausal women in the seventh decade, although recent reports have identified a trend toward younger age at diagnosis.

2 Aetiology

There are two distinct aetiopathogenic pathways leading to vulval cancer, associated with either: (A) VIN of usual type (uVIN) which is human papillomavirus (HPV)-driven or (B) VIN of differentiated type (dVIN) which develops independently of HPV.

High-grade squamous intraepthelial lesion (HSIL) is the precursor lesion of warty and basaloid vulvar squamous cell carcinoma. dVIN is the precursor lesion of keratinising SCC, which is the most frequent subtype of vulvar cancer, accounting for 63–86% of all cases. Typically, SCC occurs in older menopausal women and is not associated with HPV. Among HPV serotypes, 16 is the most common; however, many other serotypes, including 18, 31, 33 and others, have been implicated. HPV DNA can be identified in approximately

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85% of intraepithelial lesions (range, 42%–100%), but is seen in only 10%–50% of invasive lesions [3].

Basaloid or warty carcinomas are associated with the well-known risk factors for cervical carcinoma, including age at first intercourse, lifetime number of sexual partners, prior abnormal Pap smears, smoking, lower socio-economic status and chronic immune-suppression. Keratinising SCC vulva is linked to chronic vulvar inflammatory lesions, such as vulvar dystrophies, including lichen sclerosus, lichen planus, lichensimplex chronicus, squamous cell hyperplasia and differentiated VIN (dVIN) [4].

3 Pre-Invasive Disease of the Vulva

Squamous premalignant lesions of the vulva were first recognised a century ago, and since the initial description, numerous terms and classification schemes have been proposed. Bowen's disease was first described by the dermatologist J.T. Bowen in 1912. The 1976 International Society for the Study of Vulvovaginal Disease (ISSVD) endorsed the term 'squamous cell carcinoma in situ' and 'hyperplastic dystrophy'. The latter was further qualified by mild, moderate or severe atypia. The term 'intraepithelial neoplasia' was first proposed by Richart in 1967 and subsequently by Crum in 1982. In 1986, the ISSVD adopted the term VIN which was graded as VIN I, II and III.

There is evidence accumulating that VIN 1, 2 and 3 does not exist on a biological continuum, as the classification implies. VIN 1 consists almost entirely of condyloma acuminatum and is associated with low-risk HPV types 6 and 11. VIN 2 and 3, on the other hand, are true premalignant lesions with risk of progression to vulvar cancer and are associated with high-risk HPV types. Based on these aetiological and prognostic differences, the ISSVD in 2004 removed VIN 1 due to its negligible risk for cancer progression. It proposed a 2-tier classification scheme: (A) uVIN (including lesions previously classified as VIN 2 and VIN 3) and (B) dVIN. uVIN was subdivided into warty, basaloid and mixed types [5].

In 2012, College of American Pathologists (CAP) and American Society for Colposcopy and Cervical Pathology (ASCCP) recommended the Lower Anogenital Squamous Terminology (LAST) nomenclature, unifying the terminology applied to all HPV lesions involving the cervix, vulva, vagina, anus, perineum and penis, under two headings: (A) low-grade squamous intraepithelial lesion (LSIL) and (B) high-grade squamous intraepithelial lesion (HSIL). LSIL is equivalent to uVIN 1 and HSIL encompasses uVIN 2 and uVIN 3. The two-tier system is likely to be more reproducible and prognostic than earlier systems.

3.1 Clinical Features and Presentation

3.1.1 VIN, Usual Type

uVIN most commonly occurs in young women, in the third to fifth decades of life. Risk factors include smoking, number of sexual partners and immunosuppression. HPV infection is strongly associated with uVIN. Most patients complain of pruritus or dysuria. uVIN presents as white or erythematous macules or papules, which can coalesce to create verrucous plaques. Less commonly, the lesions can be pigmented. Over half of patients have multifocal lesions in the vulva, and 18–52% have squamous dysplasia at other ano-genital sites, particularly the cervix. Thus, all the patients with the diagnosis of VIN should undergo a thorough examination of the anogenital region with or without colposcopy and also performance of cervico-vaginal Pap smears.

The rate of progression of uVIN to invasive cancer has been reported to be less than 5%. The most important risk factors for malignant progression included advanced age and immune-compromised status. VIN recurs in approximately 13–36% of patients. In majority of the cases, it remains unclear whether the lesions represent true recurrences or acquisition of new lesions, given the 'field effect' of HPV infection.

3.1.2 VIN, Differentiated Type

dVIN typically occurs in older women in the sixth to eighth decades of life. dVIN is often associated with adjacent lichen sclerosus (LS) and/or chronic inflammatory dermatoses. In comparison to uVIN, dVIN tends to present as a unifocal lesion which may appear as focal grey-white discolouration with a rough surface, or vaguely defined thick white plaque, or an elevated nodule.

dVIN may be more likely to progress to VSCC than uVIN as dVIN may be found adjacent to VSCC in almost 40% of the cases [6].

3.2 Diagnosis

Colposcopic evaluation of the complete lower genital tract with directed biopsy should be a standard protocol in the diagnostic assessment of preinvasive vulvar disease. Colposcopy may permit identification of previously unidentified, subclinical lesions and better define the distribution of clinically evident disease and also to rule out cervical preinvasive disease. This is particularly the case if ablative treatment is being considered, either alone or in combination with excisional procedures. Biopsies are best taken with a Keyes biopsy instrument under local anesthesia in the office setting.

3.3 Treatment

Treatment is aimed at control of symptoms and prevention of progression to invasive cancer.

Surgery (excision or ablation) is the standard treatment, but this approach can be disfiguring causing physical and psychological problems and does not guarantee cure as recurrence rate is 30–60% [7]. Recently, evidence on activity, safety and feasibility of medical treatment of VIN has emerged. If occult cancer is suspected despite a biopsy diagnosis of VIN, surgical excision remains the treatment of choice.

3.3.1 Medical Treatment of VIN

Two candidate drugs identified for topical use for VIN are cidofovir and imiquimod. Cidofovir is a nucleoside analog with antiviral properties, and imiquimod is an immune response modifier. Tristram in 2012 reported a multicentre, randomised, phase 2 trial to assess the efficacy of these two topical treatments as an alternative to surgery in 180 women with biopsy proven VIN grade 3. Patients were randomly allocated to topical treatment with either 1% cidofovir gel or 5% imiquimod (one 250 mg sachet for every application), to be self-applied three times a week for a maximum of 24 weeks. 46% of women in each group had complete response at the post-treatment assessment visit 6 weeks after the end of treatment. They concluded that cidofovir and imiquimod were active, safe and feasible for treatment of VIN and were effective alternatives to surgery [8].

Long-term follow-up data of complete responders from the above trial indicated a trend towards response being maintained for longer following treatment with cidofovir than with imiquimod, with similar low rates of adverse events for each drug [9].

A Cochrane review on medical versus surgical interventions for treating uVIN concluded that topical treatment (imiquimod or cidofovir) may effectively treat about half of uVIN cases after a 16-week course of treatment. Factors predicting response to treatment are not clear, but small lesions may be more likely to respond. The relative risk of progression to vulvar cancer is uncertain. Women who undergo surgical treatment for uVIN have about a 50% chance of the condition recurring 1 year later, irrespective of whether treatment is by surgical excision or laser vaporisation. Multifocal uVIN lesions are more difficult to treat and are at a higher risk of recurrence and progression. Combined modalities may hold the key to optimal treatment of VIN [10].

3.4 Surgical Interventions

3.4.1 Wide Local Excision and Superficial Vulvectomy

Localised high-grade VIN lesions are managed by local, superficial excision with a disease-free margin of at least 5 mm. Wide local excision is mandatory if a lesion has warning signs of possible invasive cancer. Surgical excision with disease-free margins achieves a 90% cure rate for localised disease. If the margins are involved with disease, the cure rate falls to 50%, demanding very close follow-up [11].

Large, confluent lesions or extensive multifocal disease, particularly in the presence of colposcopic warning signs of early invasion, require more extensive excisional procedures with rotational flaps to fill the defect, or superficial (skinning) vulvectomy with a split-thickness skin graft.

3.4.2 CO_2 Laser Surgery

CO_2 laser ablation under colposcopic control may be the preferred treatment in young patients with large lesions in whom restoration of anatomy is desirable [12].

The initial 2 weeks following more extensive laser ablative procedures may be associated with significant pain, particularly with micturition. The use of appropriate laser technology and settings, advanced surgical expertise with careful control of depth of ablation, and appropriate postoperative care will mitigate much of the potential morbidity. CO_2 laser ablation is particularly useful in patients with periclitoral and peri-anal disease, where the preservation of anatomy and function is important.

3.5 HPV Vaccination

The FUTURE I and FUTURE II trials of the quadrivalent vaccine against HPVs 6, 11, 16, and 18 have demonstrated very high levels of protection against future development of usual-type VIN [13]. The use of vaccination against HPV 16 oncoproteins as a therapeutic strategy for women with usual-type VIN also appears very promising [14]. The combination of imiquimod treatment with HPV vaccination may offer another non-surgical approach to the treatment of VIN. A recent British Phase II trial evaluated the treatment of VIN using imiquimod followed by an HPV therapeutic vaccine (TA-CIN, Fusion Protein HPV 16 E6E7L2) [15]. Complete histologic regression was observed in 32% of women at week 10, increasing to 58% at week 20 and 63% at week 52. These results are promising and results of larger trials and long-term follow-up are awaited.

3.6 Follow-up

Treatment of VIN should be individualised according to age, distribution of the lesion, severity, associated disease and previous treatment. Close follow-up after treatment remains essential because of the risk of recurrent disease. Most recurrences occur within 3 years of treatment. Positive excision margins, multifocal disease, smoking and immune-suppression are associated with increased recurrence rates.

4 Vulval Cancer

4.1 Introduction

Malignant tumours of the vulva are rare and account for less than 5% of all cancers of the female genital tract. Squamous cell carcinomas account for 85–90% of cases, whereas melanomas, basal cell carcinomas, invasive Paget's disease, Bartholin gland carcinomas, neuroendocrine, merkel cell tumours and sarcomas are less common. Most vulval malignancies arise within squamous epithelium. Squamous neoplasms arise most commonly on the labia minora, clitoris, posterior fourchette, perineal body or medial aspects of the labia majora. Malignant melanoma of the vulva accounts for <10% of all primary malignant neoplasms on the vulva, and vulval melanoma accounts for approximately 3% of all melanomas in women. Vulval Paget's disease occurs in older women. Approximately 15% of women with vulvar Paget's disease have underlying primary adenocarcinoma, usually arising within apocrine glands or the underlying Bartholin's glands.

4.2 Clinical Presentation

Most women with vulvar cancer present with pruritus and a recognisable lesion. Less common presenting symptoms include vulvar bleeding, discharge, dysuria, or occasionally a large metastatic mass in the groin. On physical examination, the lesion is usually raised and may be fleshy, ulcerated, leukoplakic or warty in appearance. Warty lesions are often initially misdiagnosed as condylomata acuminata. Vulval Paget's disease typically presents as an eczematoid, red, weeping area on the vulva, localised to the labia majora, perineal body, clitoral area or other sites. This disease usually occurs in older women, although rarely can occur in a premenopausal woman. Vulval melanoma may arise from a pre-existing pigmented lesion or from normal-appearing skin. The primary site on the vulva may be the clitoris, labia minora and labia majora with predominant symptom as bleeding.

4.3 Pre-treatment Evaluation

Patient presenting with a suspicious lesion should undergo a diagnostic biopsy. Selecting the most appropriate site for biopsy in women with condyloma, chronic vulvar LS, multifocal VIN 3 or Paget's disease can be difficult, and colposcopic guidance with multiple biopsies may be required. Tissue biopsies should include the cutaneous lesion in question and representative contiguous underlying stroma, so that the presence and depth of invasion (DOI) can be accurately assessed. If invasion is suspected and a punch biopsy fails to confirm the clinical suspicion, then an incisional biopsy should be performed. Diagnostic excisional biopsy is to be strictly avoided, to facilitate the sentinel node procedure and fashion adequate surgical margins at the time of definitive surgery.

A detailed clinical examination with measurements of the primary tumour, assessment for extension to adjacent important mucosal or bony structures and assessment of the inguino-femoral lymph nodes should be performed. It is important to obtain pretreatment pictures and record not only the anatomical extent of lesion but also the distance from vital structures such as the clitoris, urethral meatus and anus, since these structures may be a limiting factor for obtaining adequate surgical margins. A detailed mapping is also of great assistance to plan brachytherapy after external radiation in patients where treatment is contemplated with primary radiation therapy and not surgery. Whenever needed examination under anesthesia should be done to map the pre-treatment disease extent. Careful examination of vagina, cervix and anal canal should also be undertaken to rule out multi-focality.

Suspicious lymph nodes on physical examination or imaging should be subjected to fine-needle aspiration cytology or biopsy if the findings would alter the therapeutic plan. For patients with very extensive lesions, cysto-urethroscopy and/or procto-sigmoidoscopy may be done. CT scan should be obtained in patients to known extent of inguino-pelvic and abdominal lymph node involvement. Chest X-ray should be obtained to rule out lung metastasis. PET may be useful in evaluating patients with vulvar melanoma for distant metastases. A role for PET in squamous cancer has not been established.

Staging for vulvar cancer can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 636–637, Chapter no. 50, Vulva Table: Definition of TNM and AJCC prognostic stage groups which can be accessed at https://emedicine.medscape.com/article/2156984-overview

4.4 Management

4.4.1 Principles of Management

Management of vulval cancer requires a multidisciplinary team approach. Successful centralisation of the management of patients with vulvar cancer especially in tertiary cancer centres has been shown to be associated with improved survival. Standard treatment for early-stage disease is radical wide local excision of the primary tumour with or without inguinal–femoral lymphadenectomy or sentinel lymph node mapping/biopsy. The decision to address lymph nodes is based on DOI and thickness. Stage I squamous carcinomas of the vulva with a DOI ≤1 mm are associated with <1% risk for lymph node metastasis. Tumours with a DOI of 1.1–3.0 mm are associated with lymph node metastases in 6%–12% of patients and approximately 15%–20% with a DOI of 3.1–5.0 mm [16]. Hence, all stage 1 vulval squamous cell carcinoma with DOI >1 mm should undergo inguinal–femoral lymphadenectomy or sentinel lymph node mapping/biopsy along with radical excision of the primary vulval tumour.

Lymphovascular space involvement is also associated with a higher frequency of lymph node metastasis. The International Society of Gynecologic Pathologists (ISGYP) recommended that the pathology report should include information on diameter of tumour (specifying measurement conditions), depth and thickness of tumour invasion and presence of absence of lympho-vascular space invasion. Survival is improved with postoperative radiation therapy to selected patients deemed to be at high risk for loco-regional failure. For locally advanced vulval cancers, neo-adjuvant radiotherapy with concomitant radio-sensitising chemotherapy has proven to be effective in treating vulval cancer patients for whom radical surgery would be either too morbid or to prevent urinary or fecal diversion stoma. If surgery is not envisaged after neo-adjuvant chemo-radiation, then boost radiation should be used (either brachytherapy or external) to maximise local control.

4.4.2 Stage-Wise Management

Stage I/II Tumours

Tumours ≤2 cm in Size with DOI of the Vulvar Stroma ≤1 mm

Superficially invasive carcinomas have minimal risk for lymphatic dissemination. Radical wide local excision with a 1-cm normal tissue margin is the treatment of choice. Patients in this category represent the only subset for whom inguinal femoral lymph nodal dissection can be avoided. These early superficially invasive carcinomas tend to arise in younger patients with VIN and are more likely to be associated with high-risk HPV infections.

Tumours with DOI of the Vulvar Stroma of >1 mm, >2 cm in Size

Radical wide local excision of the primary tumour or radical vulvectomy with unilateral or bilateral sentinel lymph node biopsy (SLNB) +/− inguinofemoral lymphadenectomy is now the standard treatment. The procedure removes the primary tumour with a wide radial margin of normal skin (1–2 cm), along with a deep margin to the deep perineal fascia [17]. Radical vulvectomy may sometimes be indicated for very large tumours. Vital structures like urethral meatus and clitoris should be preserved whenever possible to avoid psychosexual consequence especially in young females.

With careful planning of surgical excision and adequate tissue mobilisation, most vulvar defects can be closed primarily. With larger vulvar resections or poor tissue mobility, primary closure may not be feasible and planned vulvar reconstruction with fascio-cutaneous advancement flaps and myocutaneous flaps must be considered. A study from Kentucky analysed 122 vulval cancer patients with T1 and T2 lesions from 1963 to 2003. Radical vulvectomy was performed on 49% patients and radical hemi-vulvectomy on 51%. Inguino-femoral node metastases were present in 11% of patients with a T1 lesion and 31% of patients with a T2 lesion. Disease-free survival of patients was excellent in both the groups being 98% and 93% for T1 and T2 lesions, respectively, at 5 years. Local or distant recurrence was not more common in patients with radical local resections versus those treated by radical vulvectomy [18].

Sentinel Inguinal Lymph Node Biopsy (SLNB)

The SLNB is defined as the first draining lymph node of a tumour which can be identified by lymphatic mapping. Preliminary experience with both intraoperative lymphatic dye and radioisotope injections confirmed that the SLN of the vulva is always in the groin and can be identified in most patients [19].

This early experience formed the basis of 2 large multi-institutional trials that aimed to determine the feasibility and safety of SLNB in women with early-stage vulval cancer. The GROINS V trial that enrolled 403 evaluable women with tumours ≤4 cm who underwent SLNB alone with 623 groin dissections. Metastatic sentinel nodes were found in 163 groins (26.2%) 0.276 women had a negative SLNB and were closely observed for recurrence during a 2-year follow-up period. 2.9% of these 276 women suffered a groin relapse. When patients with multifocal primary tumours were excluded from the analysis, the relapse rate was only 2.3%. Morbidity was significantly decreased in patients undergoing sentinel node biopsy only [20].

In Gynecological Oncology Group (GOG) 173, 418 evaluable women underwent SLNB followed by unilateral or bilateral inguino-femoral lymphadenectomy depending on whether the tumour was a lateral or a midline tumour. The false-negative rate was 8.3%, and the false-negative predictive value (FNPV), i.e., was 3.7% for the entire cohort. The FNPV is a prediction of the chance of a positive non-sentinel lymph node when the SLN is free of tumour and a lymphadenectomy has not been performed. In GOG 173, the FNPV by groin was 2.7%; for patients with tumours less than 4 cm, it was 2.0%. This means that a patient with a tumour less than 4 cm, no palpable lymph nodes and a negative SLNB has a 2% chance of a positive groin node [21].

The results of these studies indicate that, for women with primary tumours ≤4 cm, no palpable groin nodes, in the care of a surgeon experienced with the technique, the risk of groin relapse following a negative SLNB is 2%–3%. Before implementing this technique as standard, each gynaecologic oncologist should determine his or her own false-negative rate by performing SLNB followed by inguino-femoral lymphadenectomy in approximately 10 cases. Ideally, all vulval cancer patients should be treated at high-volume referral centres. In both GOG 173 and GROINS V, half of the lymph node metastases were detected by pathologic ultra-staging with serial sectioning (3 sections per mm) and immunohistochemistry (IHC) with cytokeratine (AE1/AE3) if routine H&E staining did not reveal metastatic disease. Thus, SLNB has the promise of reducing the unnecessary lymphadenectomy performed in node-negative women while at the same time identifying additional women who may benefit from adjuvant therapy.

If a sentinel node is positive, the patient requires adjuvant treatment for the groin. A review of the Groningen study reported that there was no cut-off in the size of the metastatic focus in the sentinel node below which the chances of non-sentinel node metastases were close to zero [22]. If there is failure to detect sentinel node, it is important to undertake complete inguino-femoral lymphadenectomy.

Long-term follow-up of GROINNS V study with median follow-up of 105 months showed that disease-specific 10-year survival was 91% for SN-negative patients compared to 65% for SN-positive patients [23]. Also, it is important to note that the above treatment algorithm applies to patients with vulval cancer <4 cm with no metastatic groin node preoperatively. If metastasis is proven in groin nodes preoperatively, then inguino-femoral lymphadenectomy should be the treatment of choice. Unilateral lymphadenectomy may be considered in patients with well-lateralised lesions. Contralateral lymphadenectomy should be considered if ipsilateral nodes are positive.

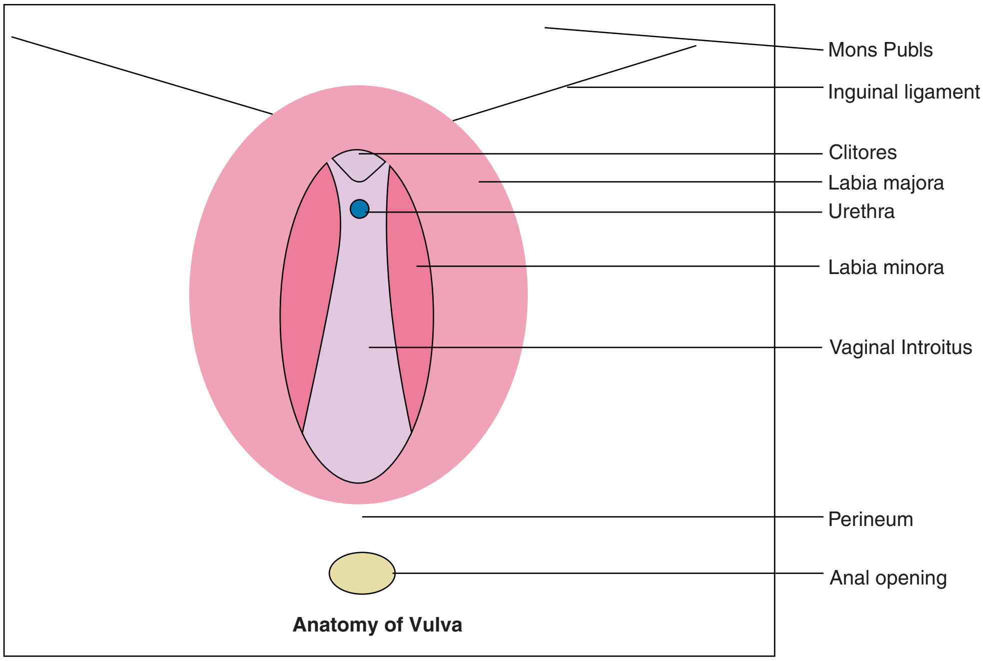
Key surgical anatomical landmarks with standard incisions for local resection of the vulval tumour and inguino-femoral lymphadenectomy are shown in Figs. 1, 2, 3, 4. Details of the steps of surgery along with surgical illustrations are depicted in Atlas of operative surgical oncology published by Tata Memorial Hospital [24].

4.5 Adjuvant Radiation

4.5.1 Primary Site

Close surgical margin portends high risk of local recurrence following. Recurrence has also been correlated to tumour size, lymphovascular space invasion and deep tumour penetration. Adjuvant radiation to vulva should be considered in patients with large tumour (>3 cm) with depth of invasion >5 mm, pathological margin ≤8 mm or other pathological high-risk features (like deep invasion and lymphovascular space invasion). In such cases, local radiation should be considered only to vulva in patients with risk features of local relapse (Fig. 5). Prophylactic postoperative groin irradiation is not recommended for a surgically negative groin.

Fig. 1 Figure depicting relevant anatomy of vulva



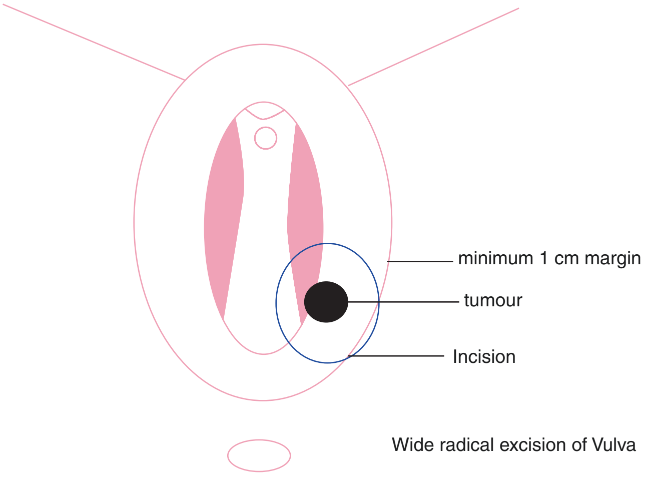


Fig. 2 Figure depicting incision for vulvar surgery

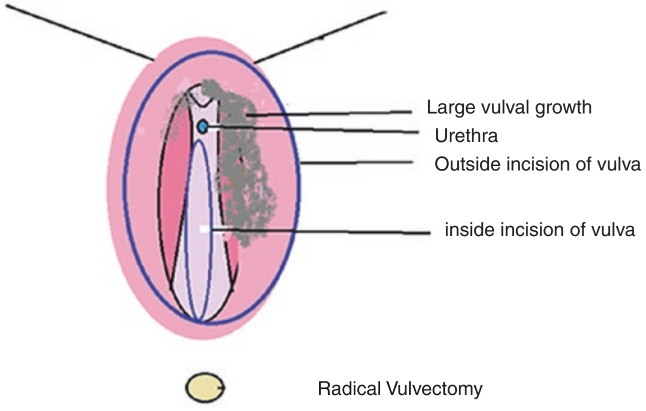


Fig. 3 Figure depicting clinical cartoon for wide radical excision of vulvar cancer

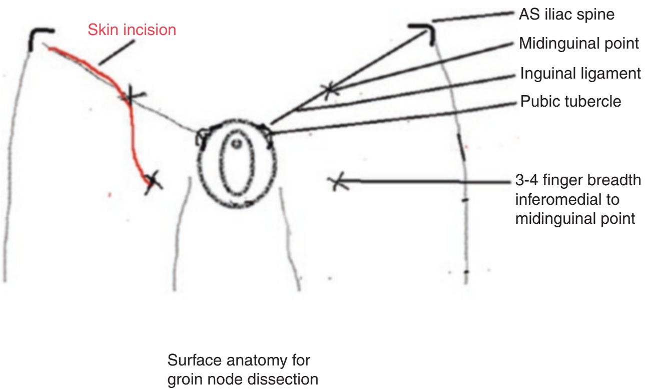

Skin incision
AS iliac spine
Midinguinal point
Inguinal ligament
Pubic tubercle
3-4 finger breadth inferomedial to midinguinal point
Surface anatomy for groin node dissection

Fig. 4 Figure depicting incision for groin node dissection

4.5.2 Nodal Irradiation

Survival benefit is reported in those with pathologically involved groin nodes with the use of adjuvant radiation. Data from GROINSS-V study indicate that adjuvant radiation may have survival benefit in patients with one positive inguinal node, as patients with sentinel node metastasis >2 mm had reduced disease-specific survival (69.5%) than those with sentinel node metastasis ≤2 mm (94.4%, $p = 0.001$) suggesting need for more aggressive local treatment [25].

GROINSS-VII study recently reported the role of radiotherapy (50 Gy/25#/5 weeks) in women undergoing sentinel lymph node biopsy and who had micro-metastases (deposits ≤2 mm); however, excessive relapse was observed with radiotherapy alone in those with macrometastasis suggesting the need of inguino femoral lymphadenectomy +/− radiotherapy in those with more than one lymph node metastasis and/or extracapsular extension. The role of addition of concurrent chemotherapy or escalated doses of radiation in the setting of SLN biopsy and macro-metastasis is presently under investigation in a separate GROINSS V study [26].

To define the optimal treatment for patients with involved inguinal nodes following radical vulvectomy and inguinal lymphadenectomy, GOG published results of 114 patients with inguinal metastases [25]. Those with involved inguinal nodes were randomised intra-operatively to receive either pelvic node dissection or postoperative irradiation to the pelvis and inguinal nodes. The patients in the radiation group had significantly improved 2-year survival (68%) than patients in the lymph node dissection group (54%; $p = 0.03$). Groin recurrence occurred in 5.1% patients in RT arm as compared to 23.6% in pelvic lymphadenectomy arm ($p = 0.02$).

Treatment portals in such case should include ipsilateral groin and pelvic lymph nodes (upto common iliac bifurcation). The lateral extent of the planned treatment field should encompass the region of surgical dissection. An example of the postoperative treatment portals is depicted in Fig. 6. If there has been invasion of overlying skin, inclusion of an additional 5 cm of the skin flaps is recommended. Adequate care should be taken to use bolus material to ensure optimal dose to the skin. While a dose of 45–50 Gy is recommended for patients with R0 resection, a higher dose is recommmended (50–60 Gy) in patients with extra-capsular extension. Also, selective gross nodal boost up to 65–70 Gy should be considered in those undergoing partial or suboptimal nodal resection. Wherever feasible intensity-modulated radiotherapy (IMRT) should be considered as it is use is associated with no reported acute or late Grade 3–4 gastrointestinal or genitourinary toxicity [27].

A recent review of the 1797 patients within the national cancer database suggests increasing use of adjuvant chemotherapy along with radiation, which was associated with reduction in the risk of death (HR 0.81, 95% CI 0.65–1.01 $p = 0.059$). Also, the median survival improved by almost 14 months (from 29.7 to 44 months) resulting in 3-year survival of 54% (as compared to 47%) ($p = 0.001$). Therefore, adjuvant chemo-radiation should be considered for patients with positive groin nodes [28].

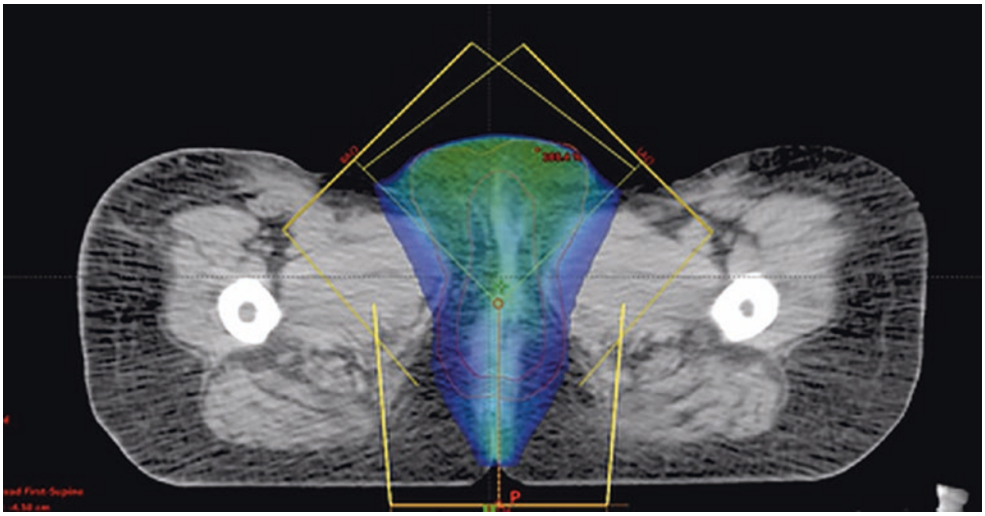


Fig. 5 Figure depicting target for vulva (postoperative) only using 3-field conformal irradiation technique

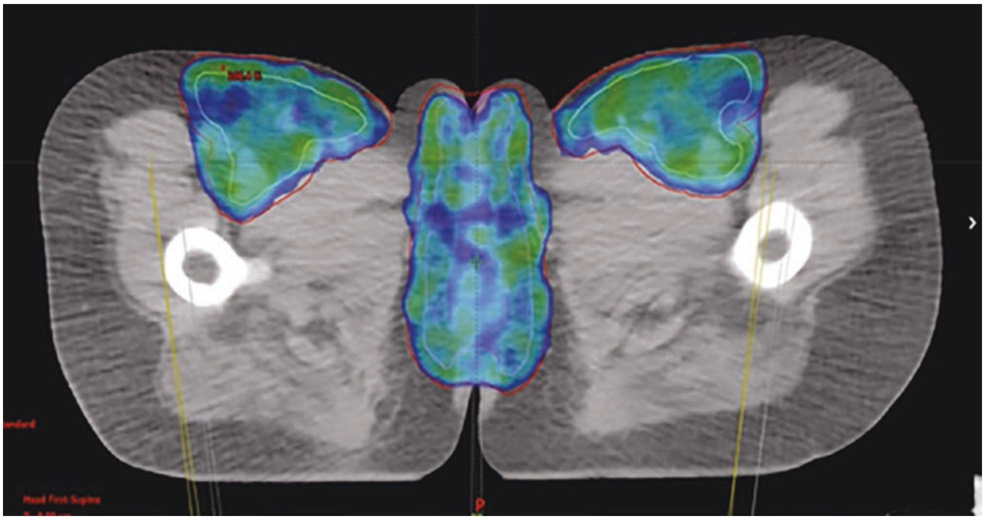


Fig. 6 Figure depicting primary and nodal irradiation for patient with locally advanced vulvar cancer using intensity-modulated radiotherapy

4.5.3 Stage III and IV

Tumours that have involved adjacent important mucosal structures (upper urethra, vagina, bladder or rectum) with or without enlarged inguinal nodes are best managed with sequenced multimodality approach. Some primary tumours may be amenable to curative resection with infralevator pelvic exenteration along with radical vulvectomy and inguinofemoral lymphadenectomy with reconstruction [29].

However, given the morbidity of upfront surgical procedure there has been increased emphasis on neoadjuvant radiation or concurrent chemoradiation followed by limited, more conservative, viscera-sparing surgery. In a Cochrane systematic review, no difference in overall survival amongst patients treated with primary or neoadjuvant chemoradiation or primary surgery [30].

GOG study that recruited locally advanced tumours used neoadjuvant chemoradiation (57.6 Gy and weekly cisplatin (40 mg/m^2)). Overall 69% patients were able to complete the planned treatment, 37 of 58 (64%) achieved a complete response and 29 of 58 (50%) had a pCR on biopsy. Following neo-adjuvant chemo-radiation for locally advanced disease, it is yet not clear whether surgery is necessary in those who achieve complete clinical response [31]. In GOG 101, approximately 70% of patients who achieved complete clinical response were found to have pathological complete response [32]. At this point, biopsies of the original tumour bed in patients who achieve complete clinical response and tailored surgical resection of the residual disease following chemo-radiation is recommended. Groin node dissection should be undertaken after neo-adjuvant chemo-radiation as inguinal nodal relapses cannot be effectively salvaged. If surgery is not feasible, then boost radiation should be used. Nodal and primary site should receive up to 60 Gy. Wherever feasible boost brachytherapy should be considered, however, should be considered in centres with considerable expertise in treating such tumours. Institutional experience published from Tata Memorial Centre reported 5-year local control and disease-free survival of 77% and 51%, respectively, with use

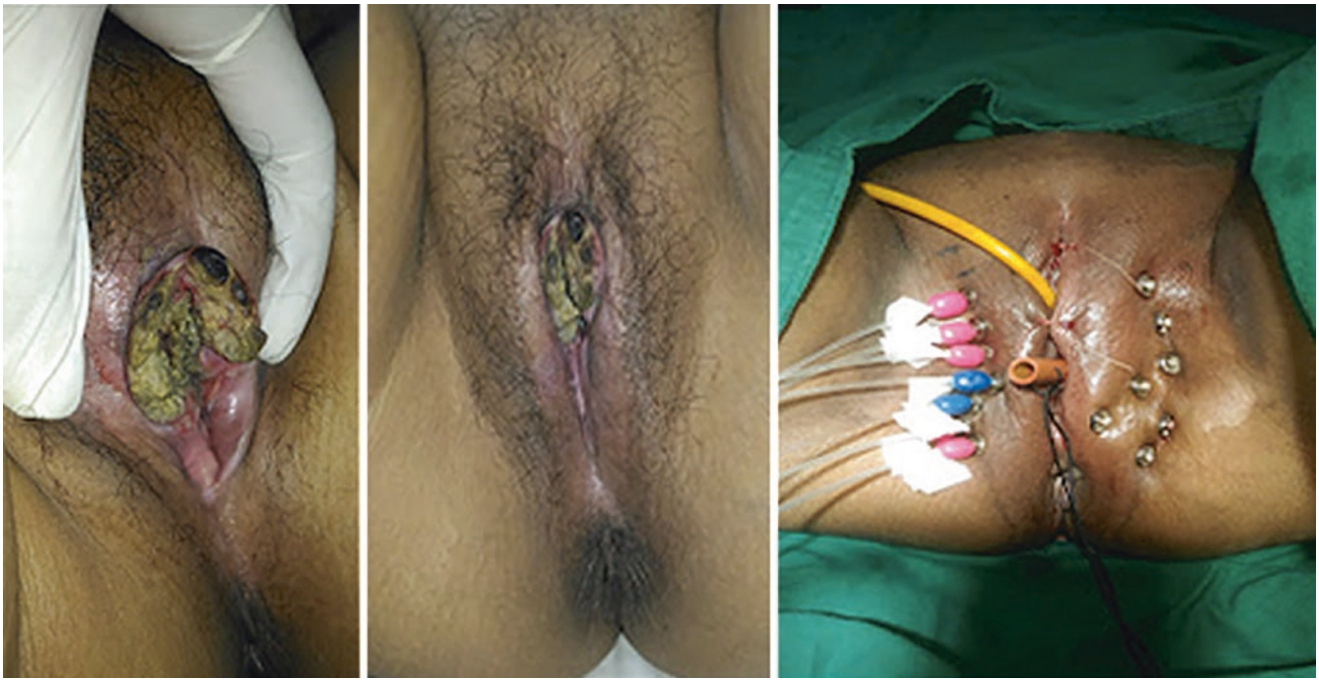


Fig. 7 Figure depicting case example of patient with vulvar cancer treated with chemoradiation and free hand interstitial brachytherapy. The composite image panel shows pretreatment lesion extent, post external radiation response and technique of free hand interstitial brachytherapy

of boost brachytherapy [33]. An example of patient undergoing chemoradiation and brachytherapy is depicted in Fig. 7.

4.5.4 Radiation Technique and Volumes

Preoperative and radical chemoradiation necessitates treatment of entire vulva, distal vagina (with adequate margins to proximal disease extent), and also nodal targets including bilateral inguinal, external, internal iliac and common iliac nodes. As the treatment target is heterogenous and complex and involves irradiating large volumes therefore advanced techniques like IMRT may provide an advantage to optimise local control and minimise toxicity. Studies using IMRT have reported no incidence of gastrointestinal or genitourinary toxicity on follow-up [34].

4.5.5 Systemic Chemotherapy

Systemic chemotherapy is recommended in patients with stage IVB disease. However, the evidence of its impact on overall survival is not clear due to small numbers. While vinorelibine, bleomycin, cisplatin and mitoxantrone have been used in various studies, at present, combination of paclitaxel and carbolatin (paclitaxel 175 mg/m^2 over 3 h and carboplatin AUC 5 over 1 h) remains the most commonly used systemic regimen for vulvar malignancies. This is on basis of its use in other primary gynaecological cancers.

One small phase II study by Horowitz et al. evaluated the efficacy and toxicity of erlotinib (150 mg daily) among patients with locally advanced, primary, recurrent or metastatic vulvar SCC. Overall clinical benefit rate was 67.5% was reported [35]. However, responses were of relatively short duration and toxicities were significant.

4.5.6 Vulvar Melanoma

Studies have shown that prognosis of patients with vulvar melanoma is worse than that of women with extragenital melanoma and squamous cell carcinoma of the vulva. Unique molecular characters of vulvar melanoma make this disease a unique subtype of melanoma.

Surgical excision is the key treatment for localised melanomas. Adjuvant radiation or chemo-radiation is used in patients with involved margins or those who cannot undergo surgery. In the pre-immune checkpoint therapy era, studies with adjuvant interferon-alfa demonstrated survival benefits in patients with regional nodal disease. But these benefits were at the cost of health-related quality of life. The targeted therapies for metastatic vulvar melanoma include those targeting B-RAF (vemurafenib, dabrafenib), MEK inhibitors (trametinib, selumetinib) and c-KIT inhibitors (sunitinib, sorafenib). The immune therapies include those targeting CTLA-4 (ipilimumab), anti PD-1 (nivolumab, pembrolizumab) and PD L1 blocking agents (atezolizumab). Combination regimens of B-RAF and MEK-targeting drugs have also been used [36, 37]. A retrospective study looking at the role of immune checkpoint inhibitors, nivolumab or pembrolizumab, in mucosal melanoma showed overall response rate of 23% in mucosal melanomas; 40% of the patients in this study had vulvo-vaginal melanoma. Hamid et al. in an exploratory, post hoc pooled analysis of

KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006, evaluated the efficacy of Pembrolizumab in mucosal melanomas [38]. The study reported a response rate of 19% in comparison to the 33% observed in non-mucosal melanomas; however, notably, 75% of the responders were still having response at the time of data cut-off. The median duration of response was 27.6 months. The results of a similar study evaluating the efficacy of Nivolumab with or without Ipilimumab in mucosal melanomas were in sync with the aforementioned study [39]. These results are better compared to outcomes with conventional chemotherapy and at present these are options have widened the armamentarium of melanoma care.

4.5.7 Recurrent Vulvar Cancer

Recurrences of vulvar cancer occur in 12–37% of patients after initial treatment, depending on tumour stage at initial diagnosis and 40–80% of all recurrences occur within 2 years of initial treatment [40]. Outcome for patients who have recurrences within 2 years after initial surgery is worse compared to patients who had recurrences >2 years after initial treatment. Surgery if feasible is the mainstay of treatment of local recurrence. Surgery with adequate margins may be more difficult with increasing tumour size, especially when the tumour is close to the anus or urethra. Also, prior surgery with altered anatomy and, in particular, earlier radiotherapy can adversely affect skin healing with increased risk of wound dehiscence or infection. Reconstruction with fasciocutaneous skin flaps or V-Y skin flaps from the upper posterior thighs may be required in many cases. Inguino-femoral lymphadenectomy is the standard treatment for the groin when recurrent disease is infiltrating >1 mm stromal depth and when groin dissection was not part of the primary treatment. The safety of the procedure should be further investigated before it is implemented in the treatment of local recurrent vulvar cancer. Pelvic exenteration may be a curative treatment option for extensive locally recurrent vulvar cancer that is otherwise untreatable [29].

Patients who are not candidates for surgical salvage and have not received previous pelvic RT may be considered for full-dose salvage chemo-radiation +/− brachytherapy. Patients who have received previous pelvic radiation may be evaluated for brachytherapy alone if feasible. In select cases, reassessment for salvage local procedure can be made after giving 3–4 cycles of salvage chemotherapy; however, in vast majority of cases, treatment needs to be individualised.

Prognosis is poor in patients presenting with groin node recurrence and combination of surgery, radiation +/− chemotherapy be used. Chemotherapy alone for groin recurrence should be considered only in palliative setting when surgery or radiation is not possible.

4.6 Summary

Early squamous cell carcinoma of vulva is generally treated with surgical excision of the local disease and prophylactic inguino-femoral lymphadenectomy. Adjuvant radiation or chemo-radiation should be used in patients with adverse risk features to maximise local control. Patients presenting with locally advanced vulvar cancers should be offered neo-adjuvant chemo-radiotherapy with surgery or primary chemo-radiation and brachytherapy to avoid morbid surgery and diversion stoma. Role of systemic chemotherapy and targeted therapy including immunotherapy is evolving and currently under investigation.

5 Vaginal Cancer

5.1 Introduction

Primary vaginal cancer is a relatively rare malignancy. It constitutes 1%–2% of all gynecologic malignancies. Tumours that involve both the vagina and cervix or the vagina and vulva are classified as cervical and vulvar lesions, respectively. As with other squamous cell cancers of the gynaecologic tract, human papillomavirus (HPV) is implicated as a cauastive factor for squamous cell carcinomas of the vagina. History of in utero exposure to synthetic oestrogen diethylstilbestrol (DES) has been linked to the development of clear cell adenocarcinoma of the vagina [41].

5.2 Pathology

The relationship between vaginal intraepithelial neoplasia (VAIN) and invasive vaginal cancer is similar to the relationship of cervical in situ carcinoma and invasive cervical cancer. Histopathologically, most of the lesions are epidermoid and demonstrate full-thickness atypical mitoses or hyperchromatism. Majority of lesions are multifocal and can involve all the vaginal surfaces. Most common site of involvement is in the superior one-third of the vaginal canal.

Invasive squamous cell carcinoma is found in 75%–95% of primary vaginal carcinomas. The majority of these lesions tend to be non-keratinising and moderately differentiated. Verrucous carcinoma is an uncommon variant of vaginal squamous cell carcinoma. It is well differentiated and has low malignant potential. Other histologies include vaginal adenocarcinoma, melanoma, clear cell carcinoma, lymphoma and sarcoma [42].

5.3 Clinical Presentation

The majority of patients with vaginal cancer are symptomatic, and vaginal bleeding is the commonest presentation. The second most common presenting symptom is vaginal discharge, which occurs in 10%–15% of patients. Other signs and symptoms that occur less frequently are pain, urinary symptoms, rectal complaints, presence of a perineal mass. Up to 20% of women may be asymptomatic at the time of diagnosis, often revealed by routine clinical or smear examination.

5.3.1 Patterns of Spread

The upper vagina's lymphatics drain to the obturator, hypogastric, external iliac and common iliac nodal groups. The lower vagina has trunks that drain to the inguinal, femoral and external iliac nodes. Vaginal cancers, particularly those that involve the posterior wall, can drain to the inferior gluteal, presacral or perirectal nodes. There are considerable crossover drainage so that any pelvic lymph node group can serve as a drainage site. Lymph node involvement in patients with stage I, II, III and IV disease has been reported in upto 6%, 26%, 78% and 83% of cases, respectively. Hematogenous dissemination may occur to lung, liver and bone.

5.4 Diagnostic Work-Up and Staging

A complete history and physical examination necessary for the diagnostic workup. Careful attention should be given to the pelvic examination. Examination under anesthesia is required to delineate the extent of the tumour and should be documented as a detailed clinical diagram. Adequate biopsies of the tumour should include biopsies of the cervix as well, to rule out a cervical primary. The workup prior to therapeutic decision should include a CECT or MRI of abdomen and pelvis and chest X-ray. Cystoscopy and proctosigmoidoscopy if there is suspicion of adjacent organs is suspected. FIGO staging for vaginal cancers is summarised in Table 1.

Table 1 International Federation of Gynecology and Obstetrics Staging System for Vaginal Cancers

I	Tumour is limited to the vaginal wall
II	Tumour infiltration into subvaginal tissue not extending to pelvic wall
III	Tumour extending to pelvic wall
IVA	Tumour extension to bladder and/or rectal mucosa and/or direct extension beyond true pelvis
IVB	Distant metastasis

5.5 Stage-Wise Management

5.5.1 Carcinoma In Situ

Many forms of therapies have been used in the treatment of VAIN, including surgical excision, carbon dioxide laser therapy, radiation therapy and topical 5-fluorouracil. None has proven superior to the others. Surgical excision is usually accomplished with a wide local excision or partial vaginectomy. Because this disease is frequently multifocal, areas of CIS may be overlooked. A Schiller mucosa test may be performed to define abnormal mucosa. If there are multiple areas of abnormal mucosa, other treatment options like vaginal brachytherapy must be considered. Treatment involves the use of an intravaginal cylinder with or without central tandem to deliver radiation to the entire vaginal mucosa. High-dose rate brachytherapy doses of 7 Gy × 5# or equivalent doses may be used weekly with dose prescribed to 5 mm from the surface of cylinder [43].

5.5.2 Stage I

Primary surgery has a limited role in the management of patients with vaginal cancer because of the radicality required to achieve clear surgical margins. In stage I disease involving the upper posterior vagina, radical hysterectomy, partial vaginectomy and bilateral pelvic lymphadenectomy can be done. Radiation therapy is the treatment of choice for most of the Patients of vaginal cancer. In most cases, a combination of EBRT and intracavitary or interstitial brachytherapy is used to achieve optimal control rates [44].

5.5.3 Stage II–III

Concurrent chemoradiation and brachytherapy is the treatment of choice for stage II and III disease [45]. External-beam therapy involves treatment of vagina, perivaginal tissues, paracolpos (cervix if disease reaching close to cervix), pelvic and medial inguinal lymph nodes. Lateral inguinal lymph nodes are treated in patients with involved inguinal lymph nodes. Doses of 4500–5040 cGy/25–28 fractions are given to the pelvic field followed by vaginal or interstitial implant, which is guided by disease extent at baseline and at time of brachytherapy. The brachytherapy dose to the target should be modelled based on the residual disease at the time of brachytherapy and organ at risk tolerance. The aim should be to deliver upto 70–75 Gy EQD2 to the primary disease while minimising dose to the rectum to <75 Gy. In most cases, the tolerance of bladder is not reached. While modest outcomes have been reported in many series combining external radiation and brachytherapy, more recently better disease-free survival has been

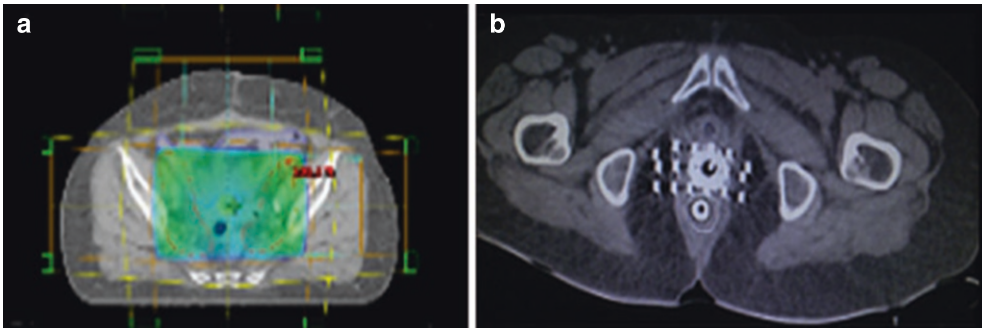


Fig. 8 (**a**, **b**) Figure depicting external beam radiation and interstitial brachytherapy technique for locally advanced vaginal cancer. Patients receive external radiation to the primary and lymph nodal drainage sites for 45–50 Gy. This is followed by intracavitary or interstitial brachytherapy is shown in panel below

reported with use of concurrent chemotherapy and integration of image-guided brachytherapy. Experience from Tata Memorial Centre using combined external radiation and chemotherapy followed by CT-based interstitial brachytherapy has been reported with 3-year disease-free survival of 64–67%. Integration of image-guided IMRT and CT-based brachytherapy is associated with 5-year DFS of 75%. Using conformal radiation and image-based brachytherapy, it is recommended that rectal doses be limited to <68 Gy to 2 cc rectal volume to minimise long-term sequelae to the rectum. Most often the optimal therapeutic ratio is achieved by combining chemoradiation with sequential fractionated interstitial template brachytherapy [46, 47]. An example of external radiation and interstitial brachytherapy is depicted in Fig. 8a, b. Recently, outcomes have been published with image-guided adaptive brachytherapy within the multicentric RetroEMBRAVE study. The study results demonstrate improved local control in T2-T4 tumours with equivalent doses >80 Gy_{10} [48].

5.5.4 Stage IVA

Individualised therapeutic management is recommended in patients with stage IV A disease. If cystoscopy reveals a small area of infiltration (<2 × 2 cm in size), then neoadjuvant chemotherapy with paclitaxel and carboplatin may be offered (2–3 cycles) followed by reassessment by cystoscopy. In patients with disappearance of fistulous communication or minimal area of fistulous communication, radical chemoradiation may be considered. Select patients may also be considered for further intra-vaginal or interstitial brachytherapy; however, treatment needs to be individualised and repeat cystoscopy may be considered prior to brachytherapy to maintain a favourable therapeutic ratio. However, if patients show no response, then palliative radiation should be considered.

Patients with a larger fistulous communication with bladder at presentation should be considered for upfront palliative radiation. Patients with fistula with rectum or sigmoid should be considered for palliative stoma followed by palliative radiotherapy.

5.5.5 Stage IV B

Palliative radiation or systemic chemotherapy should be used in patients with symptomatic stage IV B disease with principles similar to that of cervical and vulval cancers.

5.5.6 Vaginal Melanoma

The limited data available preclude definitive treatment recommendations. The overall prognosis for patients with vaginal melanoma is extremely poor, with reported 5-year survival rates of 5%–29% [48]. Distant metastases, with rates ranging from 66% to 100%, contribute to the poor outcome. While the principles of local treatment remain the same, radiation treatment should focus on use of hypofractionated radiotherapy (2.2–2.6 Gy/fraction) if radical radiation is envisaged [49]. Furthermore, advanced techniques may be used to allow delivery of differential prescription to primary target and nodes. Brachytherapy should be considered for boost in patients with response to external radiation [50]. Principles of systemic chemotherapy for vaginal melanoma should be the same as for vulvar melanomas in sections above.

5.5.7 Management of Recurrent Disease

Stage I and stage II lesions with central recurrence following previous radiation therapy might be salvaged with radical surgical procedures such as total vaginectomy, anterior or posterior exenteration or total pelvic exenteration. Likewise, early lesions that recur after limited surgical procedures could theoretically be salvaged with more radical surgical procedures or radiation therapy. Select patients who have undergone previous radiation may also be selected for re-irradiation. Patients not suitable for salvage local treatment should be considered for palliative chemotherapy and palliative care.

5.6 Summary

Radical radiotherapy and concurrent chemotherapy form the mainstay of treatment for vaginal cancers. Partial or total vaginectomy or extentration are feasible in patients either upfront or for salvage; however, they induce significant morbidity and impact on quality of life.

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Gestational Trophoblastic Disease

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Abbreviations

ActD	Actinomycin D
CM	Complete hydatidiform mole
CT	Computerized tomography
ETT	Epithelial trophoblastic tumor
GTD	Gestational trophoblastic disease
GTN	Gestational trophoblastic neoplasia
HM	Hydatidiform mole
LH	Luteinizing hormone
MRI	Magnetic resonance imaging
MTX	Methotrexate
PM	Partial hydatidiform mole
POC	Point of care
PSTT	Placental site trophoblastic tumor
TSH	Thyroid-stimulating hormone

1 Introduction

Gestational trophoblastic disease (GTD) encompasses a range of pregnancy-related disorders categorized by an autonomous overgrowth of fetal chorionic tissue or trophoblast that includes benign, premalignant disorders, complete (CM) and partial hydatidiform mole (PM); persistent, malignant disorders of invasive mole like choriocarcinoma, epithelial trophoblastic tumor (ETT) and placental site trophoblastic tumor (PSTT). Hydatidiform mole (HM) is the most common and benign subtype of the disease. The persistent/malignant forms of the disease are called gestational trophoblastic neoplasia (GTN) (Table 1).

Table 1 Classification of gestational trophoblastic disease (GTD)

Benign GTD	Malignant GTN (metastatic/nonmetastatic)
Partial mole	Invasive mole Choriocarcinoma
Complete mole	PSTT Epithelioid TT

2 Epidemiology

The incidence of GTD varies radically across the globe. The incidence is higher in Asian countries (3–10 times) compared to developed world [1, 2]. The incidence of molar pregnancy is 1 in 12/500 in Asia and Latin America and 1 in 500 in India. The incidence of GTD in various studies in India is variable and ranges between 1:190 and 1:650 deliveries. In another study by Ballal PK et al., the prevalence of GTD was 1.35 per 1000 births in a tertiary care center in Mangaluru, Karnataka, which is similar to the ones reported from northern India. The central India has reported slightly higher prevalence between 1.68 and 2.9 per 1000 deliveries [3].

After a molar pregnancy, the risk of recurrent complete and partial mole is around 1%–2% and the risk increases to 15%–20% after second molar gestation [4]. Some repeat molar gestations are due to familial or sporadic biparental molar disease which is an autosomal recessive disorder with mutations in NLRP7 (70% of cases) or KHDC3L (5% of cases) resulting in diploid complete moles [5].

About 50% cases of GTN ascend from molar pregnancy, 25% from miscarriages or tubal pregnancy and 25% from term or preterm pregnancy [6]. The incidence of GTN after spontaneous miscarriage is assessed at 1 in 15,000 pregnancies, and the incidence after a term pregnancy is around one per 150,000 pregnancies. The incidence of GTN following all types of pregnancies is around 1 in 40,000 pregnancies. Most (80%) of GTDs are hydatidiform moles, followed by 15% invasive moles and 5% choriocarcinomas (Table 2) [7].

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Table 2 Major risk factors for developing GTN (Ref. [5])

• Prior molar pregnancy
• Advanced maternal age (>40 years)
• Asian, American Indian and African ancestry
In complete mole, postmolar GTN occurs more frequently [40%–50%] in patients with one or more high-risk features, including:
• Pre-evacuation uterine size larger than dates
• hCG levels >100,000 mIU/mL

3 Clinical Presentation

The patients commonly presents with vaginal bleeding (85%). Other clinical features like excessive uterine enlargement (50%), hyperemesis and rare presentations like anemia, early onset pre-eclampsia, abdominal distension and hyperthyroidism have become less common due to early diagnosis by ultrasound [8, 9]. Partial hydatidiform moles present with vaginal bleeding or missed or incomplete abortion. Partial moles grow slowly and present later than complete moles (usually at late first or early second trimester) [9]. Choriocarcinoma has an affinity for vascular invasion and may metastasize to lung (causing hemoptysis, pulmonary embolism), to brain (causing neurological symptoms, intracranial bleed), to abdomen (causing abdominal hemorrhage, abdominal distension). It may metastasize to vagina causing a bluish sub urethral nodule, which may bleed on touch. The most common sites of metastasis are lung (80%), followed by vagina (30%), brain (10%) and liver (10%). The lung metastasis develop first followed by liver and brain metastasis [10].

4 Imaging

The first investigation of choice is transvaginal or transabdominal ultrasound; however, transvaginal is preferred due to higher resolution and closeness to the study area. Ultrasound reveals an intrauterine mass of small vesicles, which are diffusely distributed within the uterine cavity, have variable echogenicity and are typically seen as "snow storm" and bunch of grapes" [11]. These vesicles have size varying from 1 to 30 mm and epitomize the hyperplastic and hydropic villi. In addition to an enlarged uterus, theca lutein ovarian cysts may be seen on imaging.

Computerized tomography: CT scan is used for detection of metastatic disease in liver and lung. The primary disease in the uterus is seen as focal irregular hypodense lesion with or without bilateral ovarian enlargement showing multiple theca lutein cysts [12].

Magnetic resonance imaging: MRI brain is recommended for patients who are either symptomatic for brain metastasis, in case of histopathological diagnosis of choriocarcinoma or in patients with extensive lung metastasis. MRI can be used to identify the depth of myometrial invasion and the parametrial extension of local disease [13].

5 Laboratory Evaluation

Beta hCG: Elevated beta hCG is the first sign of possibility of developing GTN. Serum beta hCG level should be the first investigation in all patients with suspected GTN, in women with history of molar pregnancy or with history of abortion, or with history of normal pregnancy and also in any woman of reproductive age who presents with metastatic disease with unknown site of primary disease.

Following evacuation of a complete or partial molar pregnancy, serial serum beta hCG levels are monitored on weekly basis, until an undetectable level is reached. The diagnosis of post molar GTN should be suspected if beta hCG levels start to rise or remain elevated over several weeks. The diagnosis of postmolar GTN is as per following FIGO criteria [14]:

1. Four values or more of βhCG plateau (±10%) over at least 3 weeks: days 0, 7, 14 and 21
2. A rise of βhCG of ≥10% for 3 values or more over at least 2 weeks: days 0, 7 and 14
3. Histologic diagnosis of choriocarcinoma
4. Persistence of βhCG beyond 6 months after mole evacuation

Any woman of reproductive age who presents with metastatic disease with unknown site of primary disease and elevated beta hCG should be managed as GTN. Biopsy of metastatic lesions is not advisable as it may lead to torrential hemorrhage.

5.1 Interpretation of Beta hCG Levels

Human chorionic gonadotropin is a glycoprotein hormone with an alpha subunit similar to luteinizing hormone (LH) and thyroid-stimulating hormone (TSH) and a specific beta subunit. The sensitivity of laboratory assays to detect the beta subunit has increased substantially over years [15].

Point of care (POC) tests have monoclonal antibodies or a combination of mono- and polyclonal antibodies, which spot the intact beta hCG in urine. POC tests can detect beta hCG between 15 and 100 mIU/mL [15].

5.1.1 Phantom hCG Syndrome

It is defined as persistent mild elevation of beta hCG in the absence of trophoblastic tissue. It is seen in 2% of women of reproductive age with persistent hCG values of <300 U/mL. It is due to the existence of nonspecific heterophile antibodies in the serum which bind the assay of IgG at sites common to humans and other species, and thus mimic hCG immunoactivity, thereby causing a false-positive result. However, these large heterophile antibodies are not excreted in urine. Thus, negative urinary tests for beta hCG can exclude false-positive serum hCG values due to heterophile antibodies. This is important to avoid unnecessary intervention after successful treatment for GTN and molar evacuation [16].

5.2 False-Positive hCG

Besides phantom hCG, false-positive hCG can be found in 1% of perimenopausal and 7% of postmenopausal women. These are due to increased levels of pituitary follicle-stimulating hormone and luteinizing hormone, and due to low level of pituitary hCG secretion. Oral contraceptives can be used to stop pituitary hCG secretion [16].

5.3 Quiescent GTN

It is defined as presence of low levels of beta hCG, without any clinical or radiological evidence of disease in patients with GTD. Usually the hCG level is around 50–100 mIU/mL and remains static for 3 months. The proposed mechanism is the secretion of low stable levels of hCG by slow-growing small focus of syncytiotrophoblast cells. In absence of cytotrophoblast, these are benign, do not progress to invasion or undergo malignant transformation and do not respond to either chemotherapy or surgery [16].

5.4 Hook Effect of hCG

This phenomenon is seen when hCG is in excess and point of care tests show false-negative result as dilution step is not performed to wash the excess hCG. These falsely low or negative results occur from oversaturation of the fixed, solid-phase antibody and of the free-floating labeled antibody, which prevents sandwich formation. To avoid this effect, the lab should be asked to perform a 1:1000 dilution, with which a correct value can be obtained [17].

6 Staging and Risk Stratification

The FIGO 2000 prognostic scoring system is used to decide the systemic therapy for GTN. This score predicts the risk of developing resistance to single-agent chemotherapy. Patients with score of 0–6 are called as low risk and with score of ≥7 are defined as high risk, which specifies the risk of developing resistance to therapy (Table 3) [18]. Anatomic FIGO staging is not used for prognosis, but it signifies uniform reporting all across the globe. (Table 4) [18]. The stage of disease is represented by a Roman numeral I, II, III or IV. The risk score is represented as Arabic numerals (2, 3…). PSTT and ETT are staged according to the FIGO classification, and the prognostic score is not used in these subtype of GTN.

Table 3 WHO risk scoring system based on prognostic factors [18]

Prognostic factors	0	1	2	4
Age (y)	<40	>40	–	–
Prior pregnancy	Mole	Abortion	Term	–
Interval (mo) from preceding pregnancy	<4	4–6	7–12	>12
Pretreatment serum hCG (mIU/mL)	10^3	10^3–10^4	10^4–10^5	>10^5
Largest tumor size including uterus size (cm)	–	3–5	>5	–
Site of metastasis	Lung	Spleen, kidney	GI tract	Brain, liver
Number of metastases	0	1–4	5–8	>8
Prior failed chemotherapy	–	–	Monotherapy	Combined therapy

Low-risk score—0–6; high-risk score ≥7

Table 4 FIGO staging of GTN [18]

Stage I	Disease limited to uterus
Stage II	Disease beyond the uterus, but is limited to genital structures (i.e., adnexa, vagina, broad ligament)
Stage III	Disease extends to lungs, with or without genital tract involvement
Stage IV	All other metastatic sites

7 Management of Molar Pregnancy

7.1 Uterine Evacuation

Suction curettage is the favored method for uterine evacuation, irrespective of uterine size [19]. During evacuation, mechanical dilation of the cervix should be performed rather than using prostaglandins for cervical ripening as later is associated with excessive bleeding. It is crucial to obtain a specimen for pathology evaluation to confirm the diagnosis of HM and to differentiate between a complete and partial mole. During suction evacuation, oxytocin infusion is to be started at the time of induction in order to enable myometrial contraction, and thus reduce the chances of blood loss.

Hysterectomy may be considered for women with hydatidiform mole who are ≥40 years and do not want fertility preservation. Hysterectomy prevents the development of local invasion, but it does not eradicate the risk of metastatic disease. Hence, beta hCG levels should be monitored to ensure that persistent neoplasia does not develop [20].

7.2 Follow-up

After evacuation, all patients should undergo serial serum beta hCG testing to assess for development of post molar GTN. American College of Obstetricians and Gynecologists advise the following protocol [21]: Serum hCG every week until nondetectable (<5 mIU/mL) for three consecutive weeks, then every month for 6 months.

7.3 Prophylactic Chemotherapy

Prophylactic chemotherapy is not routinely recommended for molar pregnancy. Evidence for its use comes from RCTs and one meta-analysis. In a meta-analysis reported in 2012 [22], including three randomized trials (n = 613 patients), prophylactic chemotherapy reduced the risk of GTN by 63% (relative risk [RR] 0.37, 95% CI 0.24–0.57). However, two studies included are of poor methodological quality, and when sensitivity analyses were done excluding these two studies, the benefit of prophylactic chemotherapy was lost (59 participants; RR 0.28; 95% CI 0.10 to 0.73; P = 0). Moreover, it was observed that patients who received prophylactic chemotherapy and were later developed GTN experienced a delay in succeeding diagnosis and required more chemotherapy cycles to achieve complete response. Therefore, prophylactic chemotherapy is not currently recommended, but it may be considered in women with complete mole who are at high risk of malignant transformation and are unreliable for follow-up (like adolescents or patients from poor socioeconomic class). Chemoprophylaxis has no impact on fertility [23]. Either methotrexate or actinomycin D can be used as chemoprophylaxis.

7.4 Contraception

Women with molar pregnancy must be advised to use barrier contraception during the entire interval of hCG monitoring because the pregnancy would hinder with follow-up testing of beta hCG level and would complicate management. An intrauterine device should not be used till the beta hCG levels are within normal range as there is high risk of uterine perforation due to subinvolution of the uterus. Barrier methods or hormonal contraception are preferred. Randomized trials have established the safety of post molar use of oral contraceptives. Gynecologic Oncology Group trial (n = 266) have evaluated the safety of oral contraceptives or barrier contraception after evacuation of hydatidiform mole [24]. Both the contraceptive measures were found to be equally effective. Moreover, a systematic review of seven studies (n = 1533) has also shown no increased risk of GTN with the use oral contraceptives after molar evacuation [25].

7.5 Future Pregnancy

The New England Trophoblastic Disease Center has reported obstetric outcomes from 1965 to 2013 [26], 1388 subsequent pregnancies were seen in cohort of patients with complete mole: 68.4% term live births, 7.4% premature deliveries, 0.5% stillbirths, 18.4% spontaneous abortions and 0.8% ectopic pregnancies. Major and minor congenital anomalies were detected in 3.8% infants. 357 subsequent pregnancies were seen in cohort of patients with partial mole: 72.8% term live births, 2.2% premature deliveries, 0.3% stillbirth, 17.9% spontaneous abortions and two (0.6%) ectopic pregnancies. Major and minor congenital anomalies were diagnosed in only 15% infants. Patients with molar pregnancies should expect similar reproductive outcomes as compared to the general population.

Recurrent molar pregnancy: The estimated risk of subsequent molar pregnancy: After one molar pregnancy is 1%–1.9% and after two molar pregnancies is 15%–17.5% [4].

8 Management of Low-Risk GTN

Low-risk GTN is characterized by modified WHO prognostic score of 6 or low. Majority of patients are cured with single-agent chemotherapy, either methotrexate or actinomycin D (ActD). Several different chemotherapy regimens have been used to treat low-risk GTN (Table 5). The response rates vary among protocol due to differences in drug dosages, routes of administration, schedules and number of chemotherapy cycles delivered after normalization of hCG. The weekly intramuscular or intermittent continuous intravenous infusion MTX regimens are less effective than the daily X 5 days MTX or 8-day alternating MTX/leucovorin regimens (as evident in Table 5); hence, the latter is the preferred regimen. The weekly intramuscular MTX regimen is not adequate, particularly in patients with WHO risk score of 5–6 and in patients with histopathological diagnosis of choriocarcinoma, as confirmed in the randomized trial comparing effectiveness weekly MTX with pulsed actinomycin [30], wherein the response rate was 9%.

Actinomycin D is generally used as a second-line therapy in patients who develop resistance to methotrexate. Tolerance to actinomycin D is poor and it is associated with higher toxicities (myelosuppression, nausea and alopecia) compared to

Table 5 Chemotherapy regimens for low-risk GTN

S. no	Agent used	Chemotherapy regimen	Primary response rates (CR) %
1	8-day alternating MTX and leucovorin [27, 28]	Inj Methotrexate 50 mg IM, days 1, 3, 5 and 7; leucovorin 15 mg orally, days 2, 4, 6 and 8; recycle every 14 days until hCG normal × 6 weeks. (at our Centre MTX dose is adjusted as per body weight to 1 mg/kg, T leucovorin continues to be given as 15 mg. Methotrexate may be given IV or IM)	69
2	Actinomycin D biweekly (pulse) [4]	1.25 mg/m^2 (maximum 2 mg) IV; recycle every 14 days until hCG normal × 3 weeks	70
3.	5 days Actinomycin D [28, 29]	5 days of ActD (12 μgm/kg or 0.5 mg intravenous) repeated every 14 days (at TMH we use this regimen and cap dose of Actinomycin D to 0.5 mg/day)	88

MTX. Actinomycin D is tolerated better when given in biweekly schedule, as in the study by Osborne et al. [30]. Another protocol for ActD administration is 5-day course of Actinomycin-D 12 mcg/kg or 0.5 mg intravenously every 2 weeks. There is no difference in outcome between the two regimens of ActD [31].

8.1 Methotrexate Versus Actinomycin D

Multiple trials have compared MTX and ActD regimens for treatment of low-risk GTN, including several randomized studies and a meta-analysis [30, 32, 33] The 2012 meta-analysis included five studies concluded that ActD was associated with significantly higher cure rates than MTX (relative risk 0.64, 95% CI 0.54–0.76) without differences in toxicity [33]. However, there was heterogeneity in this analysis due to the various schedules of MTX (as a weekly injection, five-day injection and the eight-day schedule) and ActD (bi-weekly pulsed IV and the five-day IV dosing) included, number of patients involves was less (n = 517). Hence, the efficacy of actinomycin over MTX cannot be confirmed based on this meta-analysis. Another trial published after the meta-analysis (n = 62) randomized patients with low-risk gestational trophoblastic disease to MTX or ActD found no difference in complete remission rates between MTX and ActD (78 and 80%, respectively). Moreover, frequency of adverse effects was similar between the two agents [28].

8.2 Monitoring

While on treatment, serum hCG levels should be monitored every week to determine response [29]. Once the serum hCG has normalized, 3 more cycles of chemotherapy are given as consolidation to reduce the chance of recurrence [29].

8.3 Management of Resistant Disease

Resistance to first-line therapy should be suspected if there is persistent elevation of beta hCG over 3 consecutive samples or an increase over 2 consecutive samples lasting >2 weeks [26]. If beta hCG levels are low (<100 IU/L), phantom hCG must be ruled out. Hysterectomy is considered if the tumor is confined to the uterus and the patient has completed the child bearing age. If fertility is desired, salvage chemotherapy is recommended. Patients who develop resistance to methotrexate and have low hCG levels (<300 IU/mL) should be treated with dactinomycin or vice versa if actinomycin is used in first-line setting. Patients who fail single-agent treatment and presents with higher levels of hCG (>300 IU/mL), such patients should receive combination EMA-CO chemotherapy [29].

9 Management of High-Risk GTN

These patients are commonly treated with combination chemotherapy regimens, as the risk of developing drug resistance is high if single-agent therapy is used. Various protocols have been used as shown in Table 6. EMACO [Day 1: actinomycin-D 0.5 mg iv, etoposide 100 mg/m^2 iv, methotrexate 300 mg/m^2 iv, Day 2: actinomycin-D 0.5 mg iv, etoposide 100 mg/m^2 iv, folinic acid 15 mg post 12 hourly for 4 doses, Day 8: vincristine 0.8 mg/m^2 (maximum 2 mg), cyclophosphamide 600 mg/m^2] is the preferred due to its high primary remission rates and lower toxicities compared to other regimens. EMACO is the most commonly used first-line chemotherapy protocol, as shown in 2013 Cochrane review but this regimen has not been compared to other chemotherapy protocols like MAC or FAV [39].

Treatment should be continued until the hCG level becomes undetectable and remains undetectable for three consecutive weeks. At least three courses of EMA-CO should be administered after the patient achieves beta hCG levels below 5 as consolidation therapy to diminish the risk of relapse and 4 cycles are given in case of brain and liver metastasis.

Table 6 Chemotherapy regimens for high-risk GTN

Study	Protocol	No. of patients	Primary remission rates	Toxicity/mortality
Kim et al. 1998 [34]	EMA/CO (96) MA (49) MAC (40) CHAMOCA (42)	227	EMA/CO: 91%; MA: 63%; MAC: 68%; CHAMOCA: 76%	EMA/CO: 9%; MA: 36%; MAC: 32%; CHAMOCA: 22%
Bower et al. 1998 [35]	EMAC/CO	272	78%	4%
Fulop et al. 2012 [36]	EMA/CO (26) MAC (118) BEP (17)	174	EMA/CO: 81%; MAC: 93% BEP: 94%	–
Gulia et al. 2014 [37]	EMACO	22	73%	13%
Chauhan et al. 2010 [38]	EMACO	78	66%	–

9.1 Salvage Therapy

Most of the patients with GTN are cured with standard therapy; 20%–25% of high-risk patients develop resistant disease. Different platinum-based regimens should be considered in such cases. Common regimens are EMA-EP (omitting day 2 etoposide and dactinomycin and alternating weekly with etoposide and cisplatin); TE/TP (paclitaxel and etoposide alternating weekly with paclitaxel and cisplatin); ACE (dactinomycin, cisplatin and etoposide); VIP (etoposide, ifosfamide and cisplatin); BEP (bleomycin, etoposide and cisplatin); cisplatin, vincristine and methotrexate; PVB (cisplatin, vinblastine and bleomycin); ICE (high-dose ifosfamide, carboplatin and etoposide); and combinations with gemcitabine or capecitabine [38]. Response rate to second-line therapy varies from 20% to 75%, EMA /EP being the most common regimen with cure rates up to 70% [40]. Surgical resection of resistant foci of disease is important in salvage of these patients. In one series, 24 patients with high-risk metastatic resistant GTN undergoing surgical resection had cure rates of 84% [41]. Surgical procedures included hysterectomy, pulmonary resection and small bowel resection.

10 Early Mortality

Early mortality is defined as death that occurs within 4 weeks of treatment initiation. Causes of early mortality are: uncontrolled hemorrhage of highly vascularized tumors and metastases, massive pulmonary embolism, tumor lysis syndrome, sepsis secondary to chemotherapy [42, 43]. Early deaths in high-risk GTN (extensive pulmonary, hepatic and brain metastasis; FIGO score more than 12; and/or major bleeding) can be reduced by use of low-dose chemotherapy initially; etoposide (100 mg/m^2) and cisplatin (20 mg/m^2) on days 1 and 2 every week for one or two courses as shown by Charing Cross group. Use of low-dose EP has reduced early mortality from 7.3% to 0.7%. The gradual decrease in tumor volume lessens the risk of hemorrhage in vital organs and thus the mortality. Moreover, use of EP induction therapy did not increase the risk of resistance to further EMA/CO chemotherapy [44].

Vaginal hemorrhage: Significant bleeding needs urgent attention and support with blood products is to be continued until resolution. Embolization, hysterectomy and arterial ligation may be required as deferring measures till chemotherapy controls the disease, but death is very rare due to extensive vaginal bleeding [45].

11 CNS Metastasis

Initial treatment with low-dose etoposide and cisplatin is recommended to be repeated every week for 2–3 cycles. Dexamethasone is added to decrease brain r edema, and there is no role of prophylactic antiepileptic drugs. Modified EMA-CO chemotherapy is administered once patient is stabilized. The dose of methotrexate (in modified EMACO) is escalated to 1 g/m^2 over 24 h. The higher dose of MTX allows for adequate levels of MTX within the cerebrospinal fluid. Intrathecal MTX 12.5 mg is given on day 8. Modified EMACO with intrathecal MTX (without WBRT) has resulted in remission in 85% of cases [46]. Some centers use whole brain radiotherapy (3000 cGY over 10 fractions); it reduces the risk of intracranial bleeding. But there is no evidence that whole brain radiotherapy improves survival [47]. Intrathecal MTX is not given with WBRT to avoid toxicities (leukoencephalopathy).

In presence of very high-risk disease (WHO score ≥13, liver metastases along with brain metastases), EMA-EP may be considered. Inpatients with brain metastasis, the dose of methotrexate is increased to 1 g/m^2 and day 2 of etoposide and dactinomycin are omitted from the EMAEP regimen. Intrathecal methotrexate is given with the EP on day 8 [46].

12 Role of Surgery in GTN

The advent of chemotherapy and individualized protocols has made GTN a highly curable disease, surgery still plays important role in management of these cases.

1. Molar pregnancy. Suction curettage is the preferred method of uterine evacuation. Prophylactic hysterectomy may be considered for patients more than 40 years of age who are not desirous of future child bearing. Hysterectomy reduces the risk of local invasion but does not eliminate the risk of metastatic disease that can happen in 3.5% of cases [19].
2. GTN. Hysterectomy is indicated for excessive uncontrolled vaginal bleeding not amenable to uterine artery embolization or medical measures, as initial therapy in low-risk GTN when disease is limited to uterus and there is no desire to conceive in the future.
3. Surgery in chemo-resistant disease/relapsed GTN.
   (a) Hysterectomy is an option in patients who did not respond to first-line and second-line therapy and have bulk of disease limited to uterus.
   (b) Segmental uterine resection can be considered in patients with small disease (<2 cm), low hCG level and desirous of future pregnancy [48].
   (c) Pulmonary resection is the most commonly performed procedure to eliminate extra uterine metastatic disease. Best outcome seen in patients with single unilateral lesion, hCG less than 1000 IU/mL, controlled uterine disease, absence of other metastatic sites and good performance status [49].

13 Placental Site Trophoblastic Tumor

Placental site trophoblastic tumor (PSTT) is a rare form of GTN, incidence in the population is approximately 1/100,000 pregnancies constituting 1%–2% of all types of GTN [50].It is usually confined to uterus at presentation. Common site of metastasis includes vagina, lung and brain [51]. The level of serum beta hCG in PSTT does not correlate with tumor burden, hence not useful for diagnosis, treatment or follow-up. FIGO scoring is not used to determine the treatment of PSTT; hysterectomy is the preferred treatment for patients with nonmetastatic disease. Unlike choriocarcinoma, PSTT is comparatively resistant to chemotherapy. Patients with metastatic or recurrent disease are treated with combination chemotherapy EMA/CO or EMA/EP. Extra uterine spread of disease and antecedent pregnancy interval more than 4 years are poor prognostic factors [51]. The mortality rate in PSTT is 10%–20% [52].

Epithelioid trophoblastic tumors is the rarest of all GTN. Patients have moderately elevated—β-hCG (median, 665 IU/L). The common site of presentation is lower uterine segment and these tumors can be misdiagnosed as squamous cell carcinoma. The most common site of metastasis is lung. These tumors are also resistant to chemotherapy like PSTT. The only significant prognostic factor for ETT is FIGO stage. [51, 52].

14 Surveillance

14.1 Molar Pregnancy

After evacuation, weekly serum beta hCG level should be monitored until 3 consecutive weekly assays are normal. Subsequently, beta hCG levels should be checked at monthly interval for 6 months. Contraception is recommended for 6 months.

All patients with GTN are followed with weekly hCG values until undetectable for 3 consecutive weeks, and then monthly until undetectable for 12 months. For high-risk GTN some center's recommended monitoring for 2 years.

14.2 Contraception

Intrauterine device should not be used because of potential for uterine perforation. Barrier methods are preferred. Oral contraceptives are safe to use after normalization of serum β-hCG.

15 Future Pregnancy

Fertility is not affected by either single-agent or combination (EMA-CO) chemotherapy for GTN. The pregnancy rate is more than 83% after either treatment [53]. Only one study has shown slight increase in stillbirth in pregnancies post GTN chemotherapy, other studies have found no increase in abortions, stillbirths, preterm labor or congenital anomalies.

Patients with prior molar pregnancy or GTN are advised to have a first trimester ultrasound to confirm normal gestation in subsequent pregnancies. Serum hCG is measured at 6 weeks after delivery to exclude GTN. After preterm or term deliveries or after abortion in patients with prior molar pregnancy or GTN, the placenta should be carefully examined and sent for histopathological evaluation if any abnormalities are seen [54].

GTD and GTN are almost always curable as these diseases are extremely sensitive to chemotherapy drugs (except rare histologies) and presence of a highly sensitive biomarker (beta hCG), serial measurement of which has enabled early recognition of resistance or relapse so that the subsequent

Table 7 Prognosis of GTN

GTN	5 years OS	Ref.
Low-risk GTN	100%	[41]
High-risk GTN	88%–94%	[43]
PSTT		[51]
Stage I	171.3 months	
Stage II–III	70 months	
Stage IV	9.5 months	

lines of therapies can be initiated before significant tumor regrowth has occurred (Table 7).

16 Long-Term Toxicities

GTN being a highly curable disease, the key component of management is minimization of any long-term side effects. The recent study (comprising 32,244 person-years of follow-up of 1903 patients with GTDs), shows no overall increased risk of second malignancies following MTX or EMACO (if treatment duration of EMACO is less than 6 months). Patients treated with EMA-CO or with alkylating agents or cisplatin in other regimen have increased risk of second malignancies especially leukemia, oral and pharyngeal cancers, melanoma and meningioma. EMA-CO also induces menopause 3 years earlier than anticipated [55].

17 Psychosocial Issues

Women with GTN may experience anxiety, mood disturbance, sexual problems and fears over future fertility. Patient needs assessments, counseling and psychological interventions both during treatment and after remission is achieved [56].

18 Tata Memorial Centre Experience

At our center we are following the standard guidelines for the management of GTN cases (Fig. 1). Patients with low-risk GTN are treated with SA MTX at 1 mg/kg given IV on days 1, 3, 5 and 7 with oral leucovorin 15 mg single dose on days 2, 4, 6 and 8. The cycle is repeated every 2 weeks. Serum b-hCG levels are measured every week, plus before the start of every chemotherapy cycle; drug resistance is defined as any two static or one increasing value on treatment. Based on the beta hCG value patients are treated with either actinomycin D or multiagent chemotherapy. EMA/CO. Patients with high-risk GTN are started on the EMA/CO regimen. Patients who do not respond to the EMA/CO regimen are treated with EMA/EP or BEP regimens. Patients undergo hysterectomy only if there is no response to chemotherapy or if there is intractable bleeding which is not controlled by medical measures. Treatment is continued until

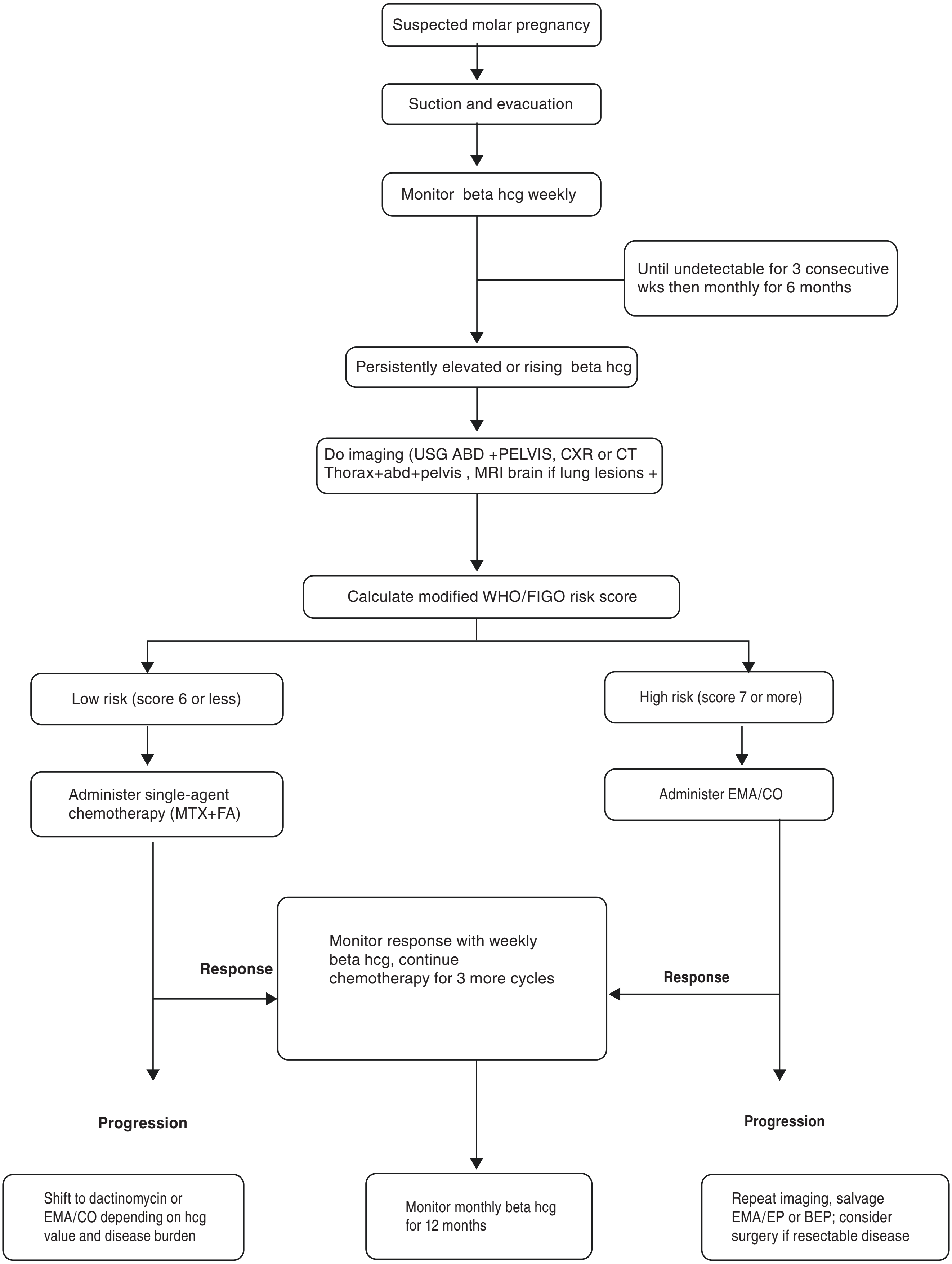
Suspected molar pregnancy
Suction and evacuation
Monitor beta hcg weekly
Until undetectable for 3 consecutive wks then monthly for 6 months
Persistently elevated or rising beta hcg
Do imaging (USG ABD +PELVIS, CXR or CT Thorax+abd+pelvis , MRI brain if lung lesions +
Calculate modified WHO/FIGO risk score
Low risk (score 6 or less)
High risk (score 7 or more)
Administer single-agent chemotherapy (MTX+FA)
Administer EMA/CO
Response
Monitor response with weekly beta hcg, continue chemotherapy for 3 more cycles
Response
Progression
Progression
Shift to dactinomycin or EMA/CO depending on hcg value and disease burden
Monitor monthly beta hcg for 12 months
Repeat imaging, salvage EMA/EP or BEP; consider surgery if resectable disease

Fig. 1 Algorithm for management of gestational trophoblastic disease

b-hCG values are normal (<5 IU/L) till three consecutive chemotherapy cycles. After the last chemotherapy cycle, patients are kept on follow-up with b-hCG monitoring consistent with standard guideline and advised contraceptive measures. Our published results are comparable to international standards [37].

19 Summary and Key Points for Management of GTN

Gestational trophoblastic disease is a disease with highest prevalence in Asian subcontinent and importantly affects young women with major implications to the families and nation as a whole. If treated adequately, there is an impressive cure rate. Hence, the future management strategies for GTDs should strategically incorporate fertility preservation as standard of care.

19.1 Diagnosis

- Reproductive-age women with either molar pregnancy or abnormal bleeding or unexplained metastatic disease: serum quantitative hCG assessment should be done [IV, A]
- Once diagnosed with GTN: patients should undergo beta hCG level, pelvic US and chest X-ray [IV, A]
- Nonmolar pregnancy or with suspicion of lung metastases in chest X-ray: CT scan chest and an MRI of the brain should be done [IV, A]

19.2 Staging

- After molar pregnancies and choriocarcinoma: FIGO scoring system should be used; [IV, A]

19.3 Treatment

- Hydatidiform mole (HM): sonographic guided suction and curettage is the essential first step of treatment.
- Indications for chemotherapy following the diagnosis of GTD:
  - Persistent or rising hCG after evacuation or
  - Histologically confirmed choriocarcinoma or
  - Distant metastasis (brain, liver or gastrointestinal tract or, lung metastasis [2 cm] or
  - Serum hCG level > 20,000 IU/l, 4 weeks after evacuation (risk of uterine perforation) or heavy vaginal bleeding or any intraperitoneal or gastrointestinal hemorrhage

19.3.1 Low-Risk Disease

- Single-agent CT (**preferred first-line regimen is MTX with FA rescue**): CT should be continued for 6 weeks after hCG normalization [II, A].
- A primary hysterectomy may be considered for perimenopausal patients with no desire to preserve fertility

19.3.2 High-Risk Disease

- MultiagentCT [IV, A]: **EMACO** is the preferred option. In patients with FIGO score >13, low-dose induction “EP” can be used to reduce the early morality [IV, A]

19.3.3 Resistant or Recurrent GTN

- Salvage therapy is effective in majority of cases.
- Surgical resection may cure the patients with solitary disease site. All other cases should be treated with cisplatin-based chemotherapy regimens like EMA/EP or TE/TP [IV, A]

19.4 Follow-Up

19.4.1 During Treatment

- Weekly serum hCG monitoring until 3 consecutive normal levels [IV, A]
- Thereafter, once a month serum hCG monitoring, for 12 months in low-risk and for 18 months in high-risk disease,
- Then 6 monthly for 1 year in low-risk and 24 months in high-risk patients,
- Then annually until 5 years [IV, A]
- No follow-up imaging tests are required [IV, A]

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Epithelial Ovarian Cancer

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1 Introduction

Ovarian cancer is among the top ten cancers affecting women around the world. Its incidence (age standardized rates) varies from per 5–9/100, 000 women in less to more developed parts of the world [1]. Its incidence in India is 4–6 per 100,000 in most states [2]. The most common subtype of ovarian cancer is epithelial ovarian cancer (90%), followed by germ cell tumors (5%) and the sex cord stromal tumors (3%–5%) [3, 4]. The common symptoms of epithelial ovarian cancers at presentation are dyspepsia, bloating, abdominal distension, and pain in abdomen, which are largely nonspecific and hence most patients with high-grade epithelial ovarian cancers are diagnosed in advanced stages across global boundaries and succumb to their disease [1]. Screening is not effective as it has not shown any significant reduction in mortality [5]. There is a common International Federation of Gynecology and Obstetrics (FIGO) staging system for all subtypes of ovarian cancer (Table 1—FIGO) and is the strongest predictor of outcome [6]. The management of ovarian cancers is multimodal with surgery and chemotherapy being

Table 1 FIGO 2014 staging of ovarian cancer

Stage I	Tumor confined to ovaries or fallopian tube(s) IA: Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings IC: Tumor limited to one or both ovaries or fallopian tubes, with any of the following: IC1: Surgical spill IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface IC3: Malignant cells in the ascites or peritoneal washings Dense adhesions with histologically proven tumor cells justify upgrading to stage II
Stage II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries IIB: Extension to other pelvic intraperitoneal tissues
Stage III	Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven): IIIA1(i) Metastasis up to 10 mm in greatest dimension IIIA1(ii) Metastasis more than 10 mm in greatest dimension IIIA2: Microscopic extra pelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes IIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
Stage IV	Distant metastasis excluding Stage IVA: Pleural effusion with positive cytology Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

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the mainstay of treatment with vital inputs from radiology and pathology for diagnosis, staging, and subtyping of tumor [3]. Radiotherapy has a limited role in the management of ovarian cancers [7]. Early integration of palliative care is needed especially in the management of advanced high-grade epithelial ovarian cancers [8]. Survivorship and fertility issues also need to be addressed in young patients with early-stage low-grade epithelial ovarian cancers [4].

2 Risk Factors

Genetic predisposition is one of the strongest risk predictors for ovarian cancer [9]. The cumulative risk of ovarian cancer up to the age 80 is 44% for BRCA 1 mutation and 17% for BRCA 2 mutation [10]. Risk reducing salpingo-oophorectomy reduces the risk of ovarian cancer by 70%–85% and also reduces mortality [11]. It should be preferable be done around 35–40 years of age after completion of family [12].

One of the hypotheses for risk of epithelial ovarian cancer is “incessant ovulation” leading to repeated trauma, repair, and thus mutations of the ovarian surface [9, 13]. Hence, factors such as increased parity and oral contraceptive use, which (give rest to) ovulation, are associated with reduced risk, while late menopause (after 50 years), hormone replacement therapy, and higher body mass index are associated with increased risk [14–16]. Tubal ligation has also been shown to have a protective effect possibly due to the fimbrial origin of ovarian cancer and distancing of the fimbria from ovarian surface by ligation [16–18]. Recently, it has been studied that these hormonal and reproductive factors and endometriosis are more commonly associated with nonserous histology like endometroid and clear cell carcinoma than serous histology [17].

3 Evaluation and Work-up

The various subtypes of ovarian cancers have different age of presentation. In women less than 40 years, the common tumors are germ cell tumors, borderline tumors, low-grade epithelial ovarian cancers, and sex cord stromal tumors. In those older than 40 years of age, high-grade epithelial ovarian cancers are most common [19]. Rarely, lymphomas, small cell carcinoma, and Ewing’s tumor are also reported [20]. A major diagnostic pitfall is metastasis to the ovary (Krukenberg) mimicking a primary ovarian tumor. The common sites of origin being stomach, colon, gall bladder, and lobular breast cancers [21]. In India, tuberculosis is also a great mimicker [22]. Hence, a careful history and a good clinical examination remain the cornerstone of evaluation. Diagnostic work-up includes an ultrasonography which may be done for initial evaluation followed by a contrast-enhanced computer tomography (CT) scan of the abdomen and pelvis for staging [23]. Tumor markers to be done depend on age at presentation. In patients presenting with disease limited to the ovary which is suspicious of malignancy, a surgical evaluation needs to be done. It is important not to biopsy the ovarian mass in early-stage disease as it would upstage the tumor. In patients with advanced disease, an ascitic fluid cytology is done to obtain a diagnosis. If cytology is nondiagnostic or there is no ascites, a CT-guided biopsy of the omental nodule, other metastatic site or the pelvic mass may be done in advanced disease.

3.1 Tumor Markers

3.1.1 CA 125

This has limited sensitivity and is not a specific marker of epithelial ovarian cancer. Any peritoneal irritation causes the CA 125 levels to rise. Hence, it may be raised even up to thousands in other malignancies (including Krukenberg tumor) or even in germ cell tumors. It may also be very high in abdominal tuberculosis or endometriosis. Hence, only high CA 125 cannot be diagnostic of epithelial ovarian cancer. Also, in some epithelial cancers like low-grade serous, mucinous and clear cell tumors CA 125 may not be raised [24].

3.1.2 CEA

It is important to do CEA levels in those with ovarian masses or ascites to rule out primary gastro-intestinal tumors. CA 125: CEA levels >25 is suggestive of primary ovarian origin [25].

3.1.3 CA 19.9

It is not mandatory to do CA 19.9 in patients with suspected ovarian cancer. However, it is important to know that it may be raised both in case of pancreato-biliary tumors as well as mucinous carcinoma of ovary [26, 27].

3.1.4 Germ Cell Tumor Markers

Alpha feto protein AFP, β HCG, S. LDH (lactate dehydrogenase).

Germ cell tumor markers should be done in women under the age of 40 years with suspected ovarian neoplasm. This is so as not to miss these highly curable malignancies. It is important to note that in young patients presenting with ascites and high CA 125 with cytology showing adenocarcinoma, it is important to still do germ cell tumor markers as it is sometimes difficult to distinguish germ cell tumors and epithelial ovarian cancers on cytology and CA125 may be high in both.

3.2 Endoscopy

In patients presenting with bilateral solid ovarian masses or those with ascites without ovarian masses, a gastrointestinal primary (GI) primary should be ruled out. An upper GI endoscopy and in those with high CEA a lower GI endoscopy should be done before making a diagnosis of primary peritoneal carcinoma in a patient presenting with ascites and no ovarian mass.

3.3 Radiology: Imaging of Ovarian Malignancies

The common imaging modalities for suspected ovarian neoplasm are ultrasonography (USG) for characterization of ovarian masses and contrast-enhanced CT scan for overall staging and detecting presence of hemorrhage and calcification. Magnetic resonance imaging (MRI) is occasionally used to better characterize ovarian masses and is usually more specific in excluding a lesion as benign, rather than the histotype of the malignant lesions.

3.3.1 USG of Abdomen and Pelvis

On USG, ovarian lesions may be seen as simple (anechoic) cysts, complicated (moving internal echoes), hemorrhagic (classical fish-net appearance), or complex (solid-cystic or with papillary projections). Doppler examination may help in assessment of vascularity of a solid lesion. Ovarian metastases (Krukenberg's tumor) usually present as bilateral solid masses. Commonest primaries are stomach, breast, gall bladder, colon, or lung.

On USG, a risk of malignancy index (RMI) score can be calculated [28]. More than 200 score is used for referring a patient to a specialized gynae-oncologist, and for supplementary MRI imaging.

$$\mathrm{RMI} = U \times M \times \mathrm{CA125}$$

*U*ltrasound (U) is based on: multilocular cysts, solid areas, metastases, ascites, and bilateral lesions. $U = 0$ (for 0 abnormality), $U = 1$ (for 1 abnormality), $U = 4$ (for 2–5 abnormalities).

Menopausal status is scored as 1 = pre-menopausal and 4 = post-menopausal

Serum CA125 is the value in IU/mL.

In a lady detected with ovarian cysts on ultrasonography, a decision to follow-up versus further evaluation varies on her calculated risk factors. A simple cyst is followed up in a low-risk woman, if it measures 5–7 cm, while in a high-risk woman, a more than 2 cm nonresolving cyst warrants follow-up assessment. A hemorrhagic cyst from 3 to 5 cm is followed at 3 monthly intervals.

3.3.2 MRI of Abdomen and Pelvis

Further assessment of USG detected findings, better predictability of benign and locoregional staging may be performed on an MRI [29]. Suspicious features on MRI are enhancing septae and solid-enhancing internal components, nodules, and projections. Locoregional adenopathy, omental, and peritoneal disease is also well seen.

3.3.3 CECT of Abdomen and Pelvis (±Thorax)

It is done at baseline for staging of ovarian malignancy (Fig. 1). It helps in better assessment of thoracic and abdominal disease, serosal and omental nodules, and adenopathy. It is also useful for response assessment in patients on chemotherapy. Response may be seen as a decrease in the size adnexal masses or a decrease in the extent of its enhancing walls, septations or mural nodular projections and a decrease in the size and number of omental caking, deposits and ascites may also be seen. Less commonly progression on chemotherapy may be seen. Response is evaluated based on RECIST 1.1 (Response Evaluation Criteria in Solid Tumors 1.1) [30]. A correlation with CA125 is a good surrogate marker for response assessment, if the levels are raised in the initial disease, and has been defined by Gynecological Cancer Intergroup (GCIG) [31].

3.3.4 Chest X-Ray

This is done at baseline to assess for any pleural effusion.

3.3.5 Mammography

In those patients presenting with only ascites, a bilateral mammogram to rule out a breast primary needs to be done, as rarely lobular carcinomas of the breast may present with ascites.

3.4 Pathological Diagnosis

3.4.1 Cytology

A vast majority of epithelial ovarian cancers, especially high-grade serous type, present with ascites. An accurate assessment of ascitic fluid sample, for detection of cancer cells, is crucial to initiate neoadjuvant chemotherapy (Fig. 2). Cell block preparations are useful to test various immunohistochemical markers to differentiate mesothelial cells from adenocarcinoma and subtype an adenocarcinoma, including of different types and grades (Fig. 3a, b) [32, 33].

The other indications of cytology in cases of ovarian malignancies include aspiration from a recurrent lesion, an accessible solid lesion, or metastatic lesions.

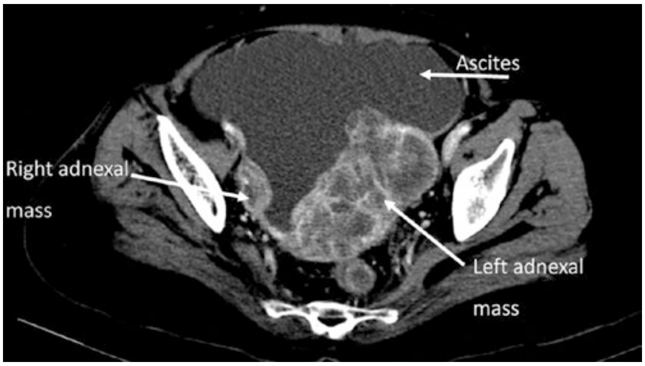


Fig. 1 Bilateral ovarian masses (left larger than right), showing heterogenous solid and cystic component, with prominent enhancing septations

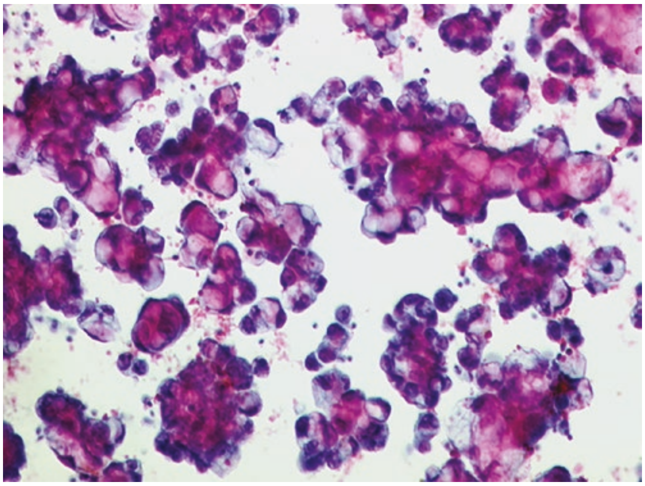


Fig. 2 Smear from ascitic fluid sample displaying several clusters of malignant cells in a case of carcinoma ovary. Papanicolaou (Pap) ×200

3.4.2 Biopsy

Image-guided biopsy is useful in planning management for women with suspected ovarian cancer. It is useful in providing a site-specific tumor diagnosis in 93% of cases. It helps in diagnosis especially in cases presenting with ovarian masses without ascites, or when there is a strong clinico-radiological suspicion of malignancy but the ascitic fluid is negative of malignancy. It is also useful in differentiating primary epithelial ovarian cancer from metastasis which might mimic it for example from breast, GI tract, etc. In patients with advanced ovarian cancer who have poor response to neoadjuvant chemotherapy, it is important to biopsy from the adnexal masses before planning second-line chemotherapy to detect any metastasis or low-grade tumors. Moreover, it is useful in situations of diagnostic uncertainty, e.g., unusual imaging patterns of disease such as peritoneal carcinoma with bilateral solid ovarian masses [34].

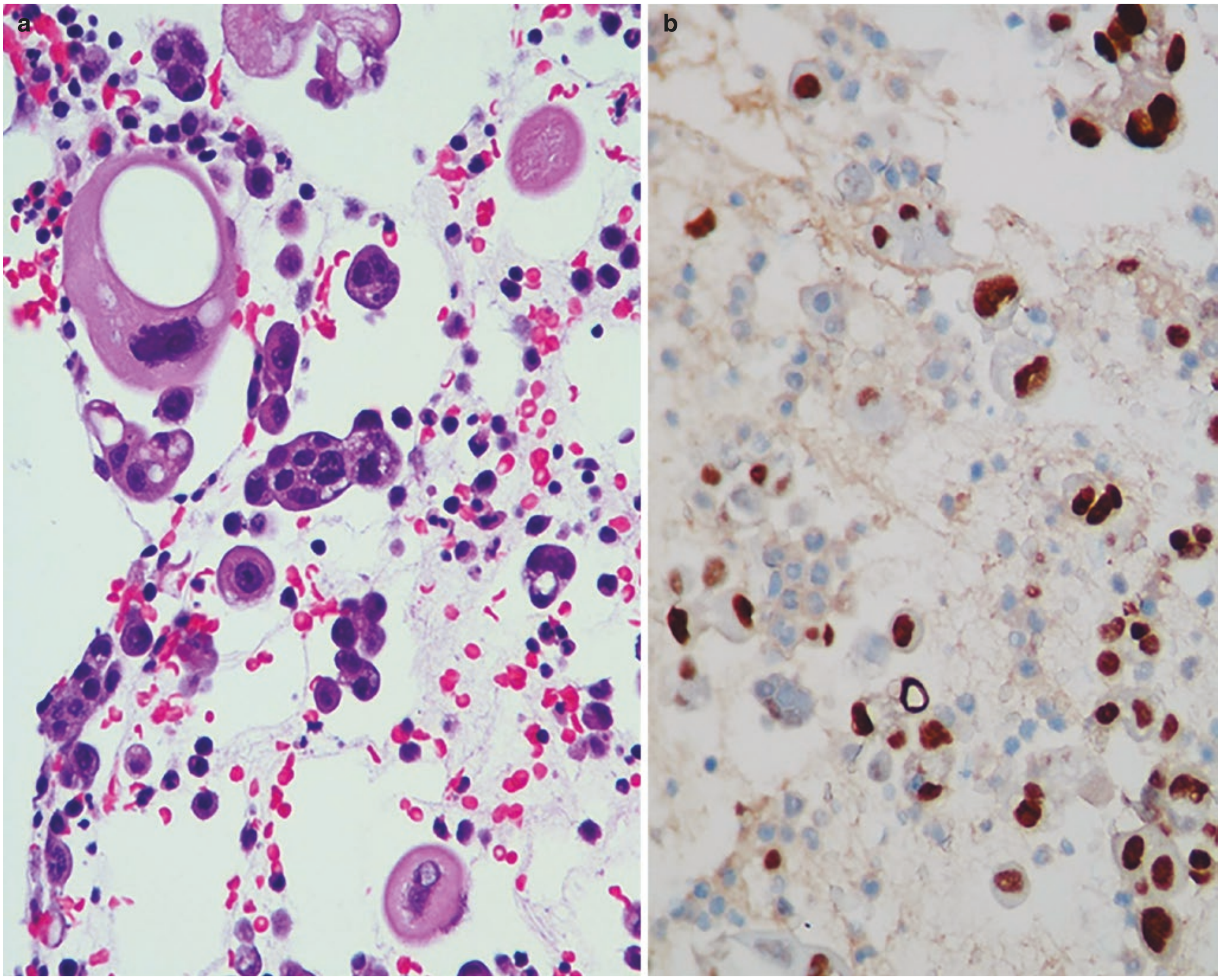


Fig. 3 Cell block preparation from ascitic fluid sample in case of an adnexal mass. Singly scattered and clusters of malignant cells, indicative of high-grade adenocarcinoma. H and E, ×400. Inset: immunohistochemical staining showing PAX8 (marker of Mullerian differentiation) positivity in the tumor cells. Diaminobenzidine (DAB), ×400

3.5 Genetic Clinic Referrals

The present ASCO guidelines recommend germline genetic testing for all epithelial ovarian cancers [35]. Although high-grade serous carcinomas are most commonly found to have BRCA 1and 2 mutations, other histologies like low-grade serous, endometroid, clear cell, and carcinosarcomas have also been found to have these mutations [35]. Germline BRCA1 and 2 mutations are found in around 13% to 15% of all ovarian cancers. Mucinous tumors of the ovary rarely have any mutations in BRCA and hence testing it is not recommended in this group. However, around 20% may have mutations resulting in mismatch repair deficiency (dMMR) [35]. Thus, testing for dMMR is recommended in mucinous tumors and also in clear cell and endometroid subtype [35]. In a recent Indian study, the incidence of pathogenic germline BRCA 1 or 2 mutation was found in 21% of ovarian and primary peritoneal cancers [36]. Among these 67% did not have family history [36]. Hence though ideally all patients should undergo germline testing, if resource constraints are present then at least those with a family history and those younger than 50 years (median age in India) should undergo testing.

4 Pathology

Ovarian tumors are classified on histopathology, based upon World Health Organization (WHO) classification, broadly into epithelial, sex cord-stromal, germ cell, germ cell sex cord stromal, hematolymphoid, and secondary tumors. Epithelial ovarian tumors are further classified as benign, borderline/atypical proliferative, and malignant [20].

4.1 Molecular Classification of Epithelial Ovarian Cancer

A "dualistic theory" is proposed for development of epithelial ovarian epithelial cancers, i.e., a distinct pathway for development of type I and type II tumors.

Type I tumors are a mixed bag which comprising of low-grade serous carcinoma, low-grade endometroid, clear cell, and mucinous subtypes (Figs. 4 and 5). Low-grade serous adenocarcinomas are characterized by the *Kras-Braf*-mediated signal transduction pathway [37]. The same genetic

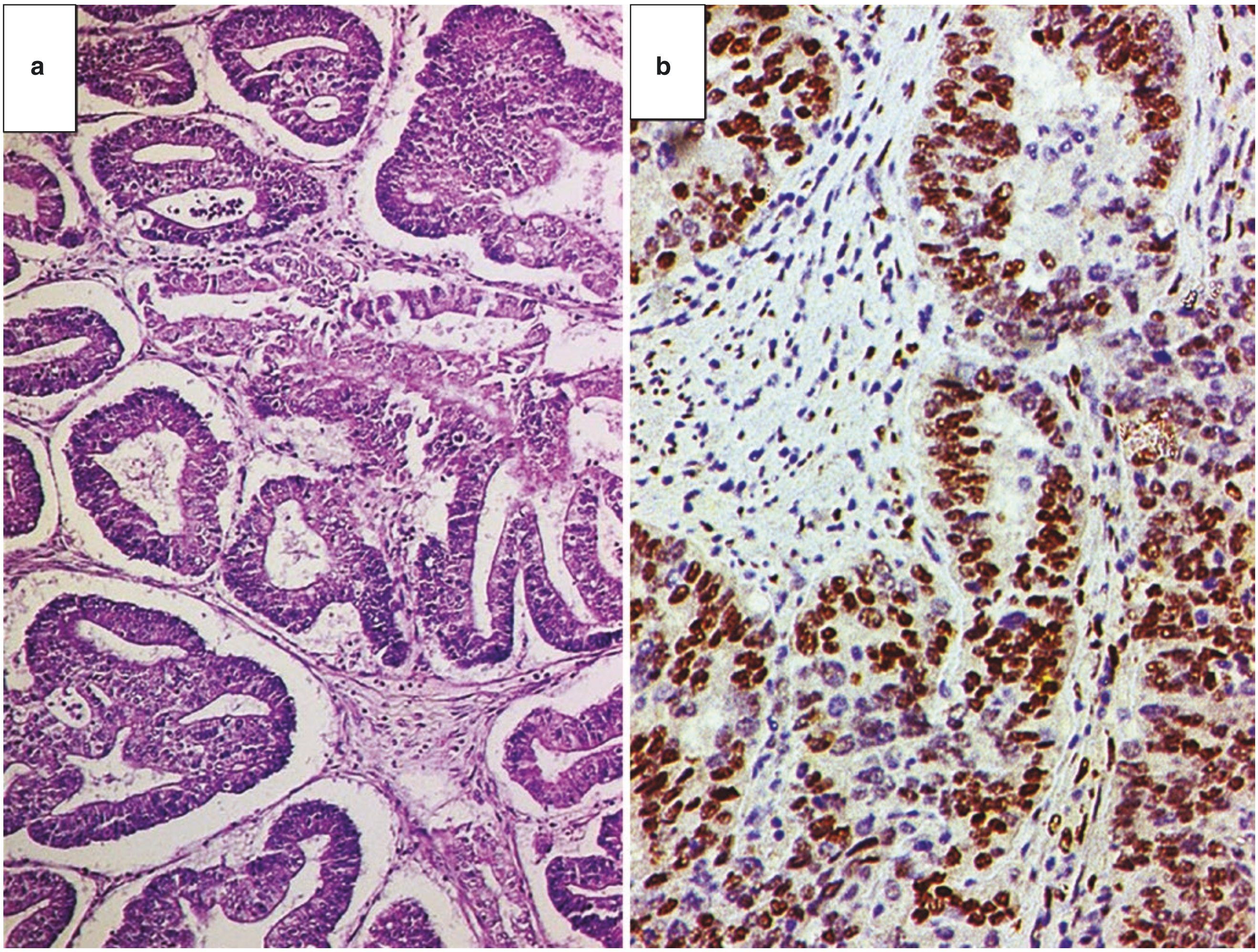


Fig. 4 (**a**) Endometrioid adenocarcinoma H and E, ×200. (**b**) Tumor cells diffuse intranuclear showing estrogen receptor (ER) positivity

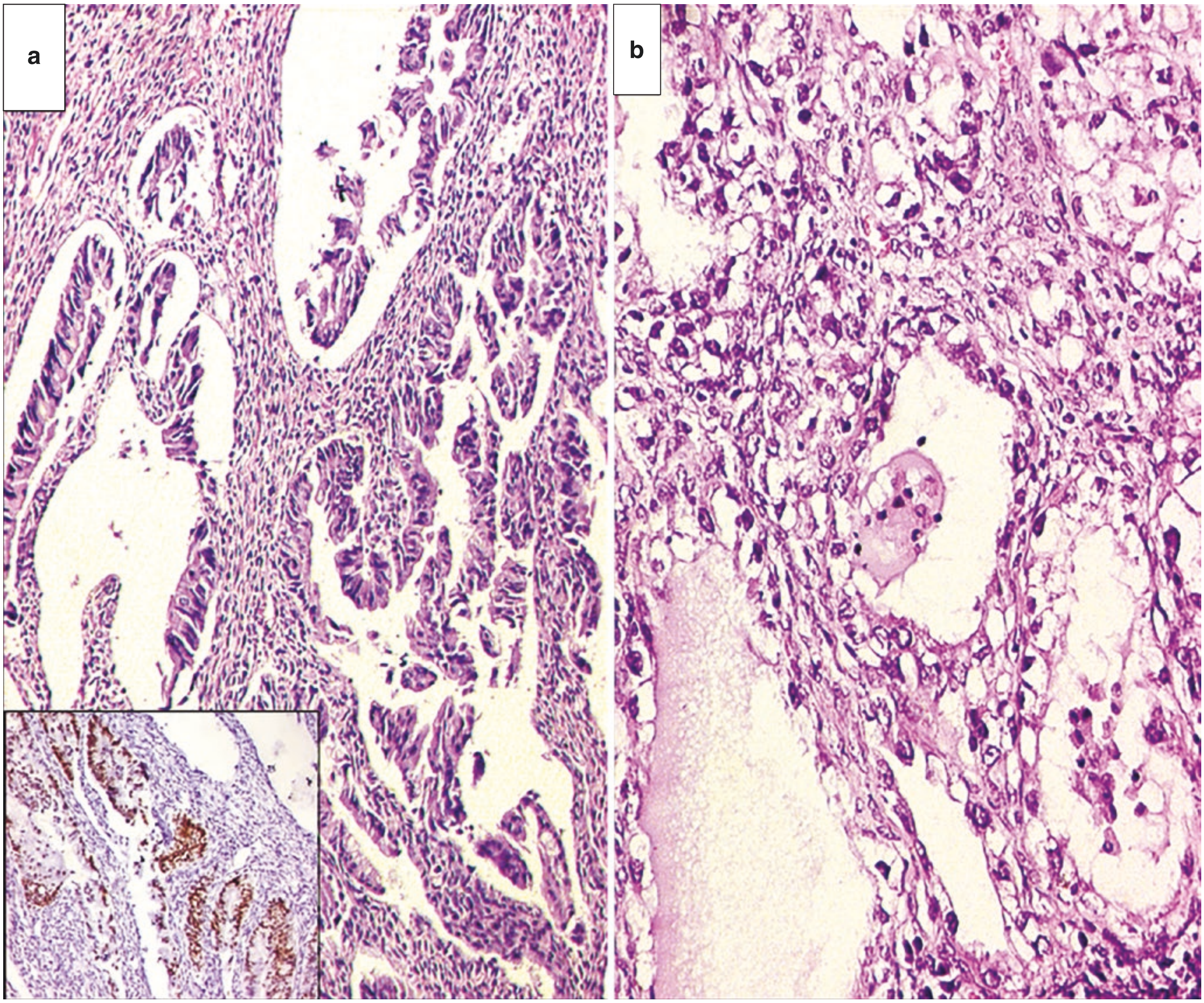


Fig. 5 (**a**) Mucinous adenocarcinoma. H and E, ×200. Inset: diffuse p53 immunostaining. DAB, ×400. (**b**) Clear-cell adenocarcinoma. H and E, ×200

mechanism underlines borderline serous ovarian tumors, from which low-grade serous carcinomas develop. Low-grade mucinous tumors are also associated with mutations in the Kras pathway [37]. The clear cell type is characterized by *PIK3CA* and *ARID1A* mutations [38–40]. In addition, alterations of genes encoding β-catenin (e.g., *CTNNB1, CDKN2A*), *PIK3CA,* and *PTEN* have also been reported in type I endometrioid serous tumors and clear cell tumors, in various studies [41–43]. Furthermore, presence of specific mutations can have an impact on treatment [39, 44].

Type II tumors are mainly composed of high-grade serous (Fig. 6), others being high-grade endometroid, carcinosarcoma, and undifferentiated carcinomas. Underlying *p53* mutation drives more than 95% of high-grade serous carcinomas [37, 38]. Inactivation of *BRCA1* and 2 genes either by mutation or inactivation of expression by promoter methylation are seen in nearly 45% of cases.

Thus, the low-grade and high-grade ovarian cancers have distinct pathways of development and usually low-grade tumors do not progress to high grade [37].

Integrated genomic analysis has led to a greater understanding of high-grade serous carcinoma and mechanisms of resistance [45, 46]. The four TCGA subtypes differentiated, immunoreactive, mesenchymal, and proliferative have different survival outcomes [45]. The differentiated and immunoreactive subtypes have better outcomes than mesenchymal and proliferative. The proliferative subtype has shown survival benefit with the addition of bevacizumab (anti angiogenic) to chemotherapy [47]. Thus, the different subtypes would hopefully also provide better understanding of the

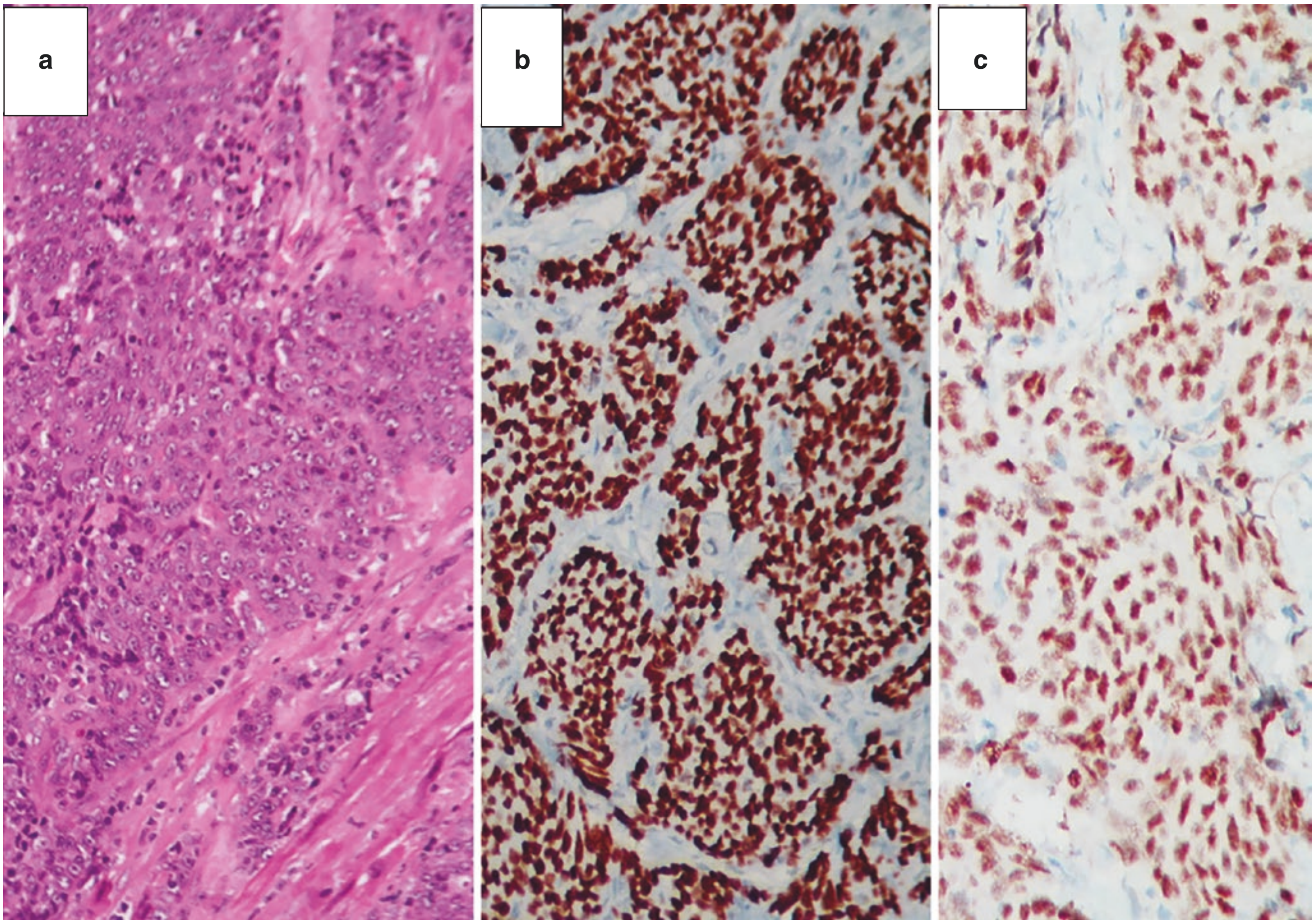


Fig. 6 (**a**) High-grade serous adenocarcinoma. H and E, ×200. (**b**) Diffuse, intense intranuclear p53 positivity, indicative of p53 mutation. (**c**) Intranuclear WT1 positivity, reinforcing serous subtype in this case

likelihood of benefit from different targeted therapy and immunotherapy in future.

There is also greater understanding of mucinous tumors of the ovary [48, 49]. Once Krukenberg tumor has been excluded, primary mucinous tumors of the ovary have now been classified into expansile and the more aggressive infiltrative subtypes which have been integrated into therapeutic decision making [3, 48]. While Kras mutation is found in all mucinous tumors, the more aggressive subtype has p53 mutations [48]. HER 2 amplification and MSI (microsatellite instability) in some of these tumors may provide a possible therapeutic target [48]. Thus, an understanding of the biology would provide a better insight on treatment strategy.

5 Borderline Ovarian Tumors

Borderline ovarian tumors (BOTs) constitute around 15%–20% of all epithelial tumors [50]. As the name suggests BOT are tumors which do not have any ovarian stromal invasion and are thus different from carcinomas which invade the stroma. They are therefore of low malignant potential and were previously called "semi malignant" [51]. Peritoneal disease present in BOT is referred to as "implants" [51]. The term borderline is based on the pathology of the primary ovarian tumor. Thus, borderline ovarian tumors may be associated with noninvasive or invasive implants (i.e., peritoneal, or omental implants invading its surrounding stroma). Serous borderline tumors of the ovary with invasive peritoneal implants are considered as low-grade serous carcinoma [3, 51].

An expert pathologist and extensive sectioning of ovarian tumor during frozen section and final histopathological reporting are important for a correct diagnosis of BOTs. Absent stromal invasion is the principal diagnostic criterion for BOTs but micro-invasion may be seen cut off (5 mm) [20, 52]. Another important pathological feature is the presence of micropapillary pattern which confers a poor prognosis and an increased risk of invasive carcinoma [51]. BOT are subdivided into serous, mucinous, endometrioid, clear cell, transitional cell, and mixed epithelial cell BOTs. Serous BOTs (67%) and mucinous (30%) BOTs are the most common subtypes. Peritoneal implants can be either invasive or noninvasive; noninvasive implants are common and share similar characteristics as primary BOT, whereas invasive implants show features like infiltrating adenocarcinomas and are considered as low-grade carcinoma. Invasive implants are most commonly seen with serous BOTs (~30%) and rarely with mucinous BOTs (3%–4%) [53, 54]. The presence of lymph node implants does not confer a worse prognosis [51].

BOT occur in younger women (a decade earlier) than epithelial ovarian cancers. They are difficult to diagnose preoperatively using radiological methods or tumor markers like CA 125 which may be raised even in borderline tumors [3, 51].

Surgery is the mainstay of treatment for BOTs. Complete staging includes complete inspection and palpation, cytology, resection of all suspicious tissue, bilateral salpingo-oophorectomy, total hysterectomy, omentectomy, and multiple peritoneal biopsies [52, 53]. The role of hysterectomy and lymphadenectomy is still controversial and may be avoided. Degree of residual disease is the most important prognostic factor in BOTs and has been studied in the ROBOT study (The Retrospective Multicenter Outcome Survey in Borderline Tumors) [55]. Fertility preserving surgeries involving preserving one ovary and uterus may be offered in young patients desirous of fertility. There is an increased risk of recurrence (especially > IA) and needs to be discussed before surgery [3]. The overall survival is, however, not different as most recurrences are borderline [3, 51] and can be salvaged. In women who have been incompletely staged with an incidental diagnosis of BOTs after surgery, role of restaging is still debated. It may be considered in those who have had only a cystectomy and on pathology there is micropapillary pattern or microinvasion or incomplete excision of peritoneal implants [56, 57].

Adjuvant chemotherapy is not indicated in BOT irrespective of stage or lymph node involvement or presence of micropapillary pattern [3, 51–53].

In borderline ovarian tumor with invasive implants, however, the role of adjuvant chemotherapy is debated. Though this group of tumors have a higher rate of recurrence (around 40%) and has now been termed as low-grade serous carcinoma, these are two distinct entities [51, 58]. Though not chemo-sensitive, the response rate to chemotherapy in patients with advanced stage is reported around 60% [58, 59]. The role of adjuvant chemotherapy is unclear, the current consensus favors observation [3, 60]. However, in patients with advanced stage, with residual disease and invasive implants adjuvant chemotherapy is an option.

They have an excellent 5- and 10-year survival rates (97%–99% and 70%–95%) in contrast to their malignant counterparts but late recurrences (15%–20%) may occur especially in serous BOTs. These patients therefore need long-term follow-up. They may recur either as BOTs (70%–80%) or as invasive carcinoma (20%–30%). Complete cytoreductive surgery with complete excision of all visible disease forms the mainstay of treatment even in recurrences [53, 61, 62].

Thus, the mainstay of treatment of BOT is surgery which achieves long-term cure in most patients.

6 Epithelial Ovarian Cancer

6.1 Principles of Management

Surgery and chemotherapy are the mainstays of management in epithelial ovarian cancers. Ovarian cancer is not one disease as already discussed and though today most subtypes are treated similarly this may change in future. Hence, it is important to note the subtype of the cancer when available. The stage of cancer is based on The FIGO 2014 classification (Table 1). Early-stage ovarian cancers undergo primary debulking surgery followed by adjuvant chemotherapy where indicated. Advanced stage ovarian cancers can undergo either neoadjuvant chemotherapy (NACT) followed by interval debulking surgery and adjuvant chemotherapy or primary debulking surgery followed by adjuvant chemotherapy (Fig. 7). There is less surgical morbidity with equivalent results for both progression-free and overall survival with the use of NACT compared to adjuvant. Hence, in patients with advanced ovarian cancers especially in those with pleural effusion, poor performance status, and low albumin neo adjuvant chemotherapy is preferred.

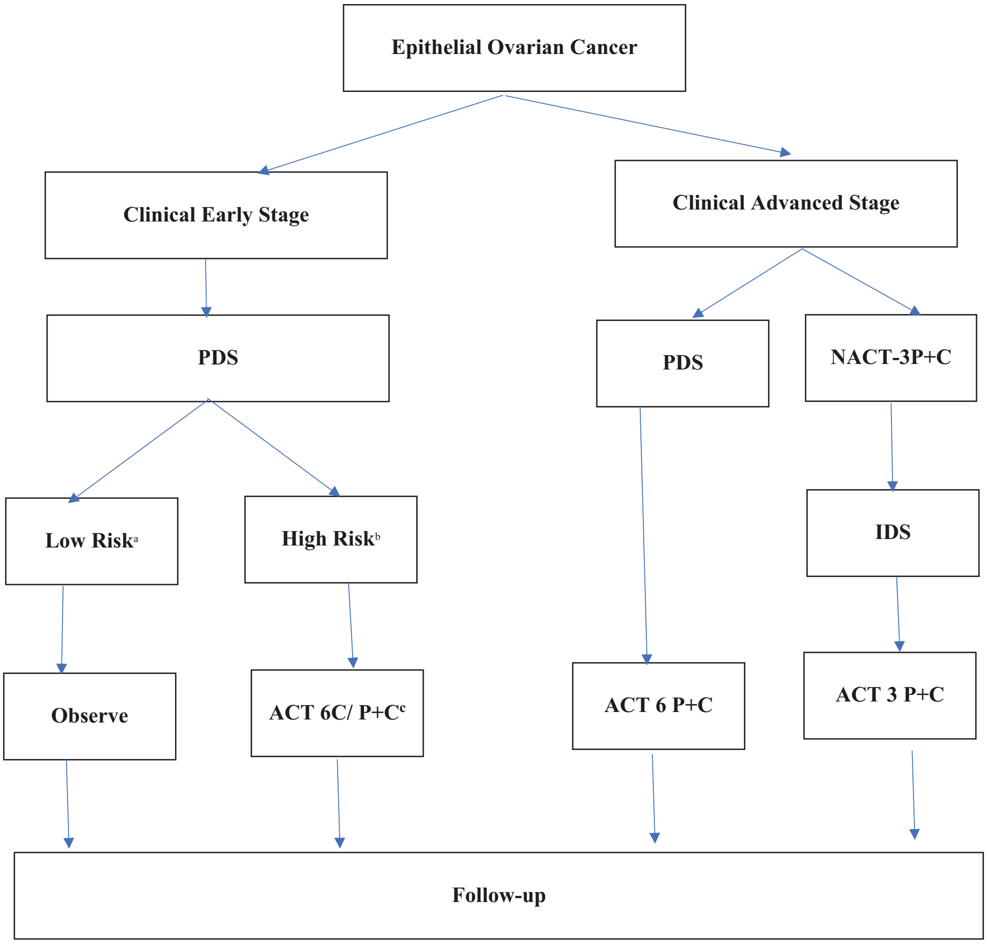
6.2 Surgical Management

Surgery plays an important role in management of all phases of ovarian cancer. Surgery may be required for histological diagnosis, stage determination, cytoreduction in primary and recurrent settings, symptom relief, and palliation of bowel symptoms (Table 2).

6.2.1 Principles of Surgical Staging for Ovarian Cancer

Surgery for ovarian cancer requires experienced and skillful surgeon with understanding of pattern of disease spread. The surgeon should take into consideration patient's wish for future fertility and histological subtype of ovarian cancer. Laparotomy is the standard surgical approach. Minimal access surgery for surgical staging of early ovarian cancer is experimental and should not be offered outside a clinical trial.

Laparotomy with a vertical incision is recommended. Incision must be adequate to evaluate the entire abdominal



[a] Early Stage Low Risk – Stage IA/IB, Grade 1, non-clear cell histology

[b] Early Stage High Risk – Stage IA/IB, Grade 2/3, clear cell histology, Stage IC, Stage II

[c] Six cycles single-agent carboplatin OR paclitaxel and carboplatin (may consider either single-agent C or 3 cycles P+C in non-serous histology)

Fig. 7 Management of epithelial ovarian cancer algorithm

Table 2 Terminology for common surgical procedure used in cancer ovary

Staging surgery—surgery performed in clinically early-stage disease to know the extent of disease.

Primary cytoreductive surgery/primary debulking—initial surgery to establish stage, diagnosis, and maximal tumor debulking before initiation of chemotherapy in patients with advanced disease.

Interval cytoreductive surgery/interval debulking surgery—cytoreductive surgery after neoadjuvant chemotherapy (after biopsy or after suboptimal surgery).

Secondary cytoreductive surgery—surgery in patients with recurrent ovarian cancer after complete primary treatment, which includes primary surgery with or without chemotherapy, and a disease-free interval.

Palliative surgery—surgery performed to relieve symptoms.

cavity. On opening the abdominal cavity if free peritoneal fluid is found, it should be collected for cytology after estimating the amount. In case fluid is not present, liberal peritoneal washings should be collected from pelvis, paracolic gutters, and subdiaphragmatic area. Careful inspection and palpation of all peritoneal surfaces including diaphragm, paracolic gutter, bladder and cul-de sac peritoneum, serosa and mesentery of bowel, and retroperitoneum should be done and documented.

All effort should be made to remove the ovarian mass intact as rupture of ovarian lesion will lead to upstaging of disease. Bilateral salpingo-oophorectomy and hysterectomy should be performed. For patient desiring fertility, unilateral salpingo-oophorectomy or bilateral salpingo-oophorectomy with preservation of uterus can be done in selected cases with early invasive epithelial ovarian cancer and borderline tumors. Availability of intraoperative frozen section is an important tool in intraoperative management of these patients. It provides information regarding nature of ovarian mass and histological subtype and thereby assists in deciding the extent of surgery. At our center, frozen section is routinely used for intraoperative evaluation of suspicious adnexal masses. In a retrospective evaluation of 217 patients with suspected ovarian neoplasms who underwent primary surgery at our institution, frozen section showed sensitivity of 100%, 93.5%, and 45.5% for benign, malignant, and borderline tumors, respectively. The corresponding specificities were 93.2%, 98.3%, and 98.5%. The overall accuracy of frozen section diagnosis was 91.2%. The majority of cases of disagreements were in the mucinous and borderline tumors [63].

Omentum should be removed as part of staging surgery. Any suspicious lesion should be excised and sent separately for histopathological examination. Random, multiple peritoneal biopsies from cul-de-sac, right and left pelvic side walls, and right and left paracolic gutters and under-surface of diaphragm should be taken if there is no gross disease seen beyond ovaries. Bilateral pelvic and para-aortic lymph node dissection is recommended in early stage though no benefit proven in advanced stages. A randomized trial comparing systematic lymphadenectomy with lymph node sampling in patients with epithelial ovarian cancer macroscopically confined to the pelvis showed that systematic lymphadenectomy led to upstaging of disease in 13% of patients [64].

6.2.2 Surgery for Early Ovarian Cancer

A large majority of early ovarian cancer patients present as "suspicious adnexal mass" on pre-surgery work-up. The purpose of surgery for suspected ovarian cancer is to establish the diagnosis, to accurately stage the disease and to select patients for adjuvant treatment. Optimal staging of early ovarian cancer may lead to upstaging of disease in approximately 30% cases [65]. Staging surgery is indicated for all ovarian cancer patients including borderline tumors.

6.2.3 Surgery for Advanced Ovarian Cancer

Surgery plays an important role in the management of ovarian cancer even with widespread disease. Surgical debulking is technically feasible in majority patients with ovarian cancers because spread of cancer cells follows peritoneal borders of abdominal cavity without deep invasion.

Primary Debulking Surgery

Primary debulking is the cornerstone in surgical management of advanced ovarian cancer, but it has survival advantage only when it leads to optimal cytoreduction, i.e., nil, or minimal residual disease (Table 3). The most important prognostic factor under control of operating surgeon is the amount of residual disease at the end of cytoreductive surgery. Therefore, every effort should be made to remove all gross disease from all sites and achieve optimal cytoreduction (nil or minimal gross residual disease). Patients with advanced ovarian cancer with low volume disease should undergo complete cytoreduction with hysterectomy, bilateral salpingo-oophorectomy with infra-gastric omentectomy between hepatic flexure and splenic hilum. Suspicious and enlarged nodes should be resected. However, systemic pelvic and paraaortic lymph node dissection does not offer survival benefit in patients with advanced ovarian cancer who do not have clinically suspicious nodes [66].

Table 3 Terminology used for completeness of surgery for ovarian cancer

R0 resection—Complete removal of all visible tumors to no macroscopic residual disease
R1 resection—Minimal residual macroscopic disease with individual tumor size ≤1 cm
R2 resection—Suboptimal debulking surgery—gross residual disease resulting in macroscopic disease >1 cm

In patients with high-volume disease procedures that may be required for optimal cytoreduction may include bowel resection, appendectomy, stripping of diaphragm and peritoneal surface, splenectomy, partial cystectomy, partial hepatectomy wedge gastrectomy, and distal pancreatectomy. Extensive involvement of upper abdomen may hinder optimal debulking of tumor hence aggressive upper abdominal surgery should be performed only when entire tumor can be removed with acceptable morbidity. Minimal access surgery may help in evaluating feasibility of optimal cytoreduction in patients with newly diagnosed ovarian cancer. For selected patients, placement of intraperitoneal catheter can be done at the time of initial surgery for adjuvant intraperitoneal chemotherapy.

Patients who are not suitable for upfront cytoreduction should be treated with neoadjuvant chemotherapy. Table 4 shows important factors that may favor neoadjuvant chemotherapy over upfront cytoreductive surgery for patients with advanced ovarian cancer. In patients with stage IIIC disease with omental metastasis of less than 5 cm primary debulking surgery may be considered [67].

Interval Debulking Surgery (IDS)

Neoadjuvant chemotherapy followed by interval debulking surgery (IDS) is an alternative treatment approach for patients with advanced ovarian cancer where upfront surgery is not feasible or unlikely to result in optimal cytoreduction. Surgery is generally done after 3 or 4 cycles of neoadjuvant chemotherapy. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy with excision of all

Table 4 Factors in favor of neoadjuvant chemotherapy in advanced ovarian cancer

Disease related *Unlikely to achieve optimal cytoreduction*	**Patient related**	**Availability of Infrastructure**
• Stage IVB disease • Bulky upper abdominal disease • Extensive peritoneal carcinomatosis • Extensive bowel wall involvement requiring >1.5 m of bowel resection or multiple bowel resections are anticipated • Disease at porta hepatis/superior mesentric artery • Disease at root of small bowel mesentery	• ECOG PS ≥2 • Elderly • Low albumin • Recent venous thromboembolism • Recent myocardial infarction • Multiple medical comorbidities	• Surgical expertise • Anesthesia and intensive care facilities • Interventional radiologist

visible disease should be done to achieve complete cytoreduction during IDS procedure. In a randomized phase III trial conducted by the European Organization for the Research and Treatment of Cancer (EORTC) interval cytoreduction after neoadjuvant chemotherapy for advanced ovarian cancer has shown similar survivals compared to primary cytoreduction and adjuvant chemotherapy with fewer peri-operative complications. The rate of optimal cytoreduction was 41.6% after primary surgery and 80.6% after interval surgery. There was higher postoperative deaths, infection, hemorrhage and venous complications with upfront surgery [25]. Another phase III multicenter trial (CHORUS) showed similar results with significantly higher postsurgical morbidity and mortality in upfront surgery arm without any survival advantage [68]. In our experience, optimal cytoreduction rate in patients with advanced disease after neoadjuvant chemotherapy is 81.5% with acceptable perioperative morbidity. The rates of Grade 3 or 4 intraoperative and postoperative complications were quite acceptable, 4% each. The median progression-free survival was (PFS) was 15 months and the median overall survival (OS) was 35 months in these patients [69].

Thus, the decision for neoadjuvant chemotherapy in advanced ovarian cancers is based on patient and tumor characteristics.

6.3 Medical Management

6.3.1 Principles of Systemic Therapy

Platinum-based chemotherapy has long remained the backbone of treatment of ovarian cancer. There is greater understanding now of the reason for the same. Although 15% of patients have germline BRCA mutation, around 51% have a defect in the homologous DNA repair pathway (BRCA ness) [45]. Thus, the ovarian cancer cells cannot repair the DNA damage (adducts) caused by platinum leading to cell death. This is the reason for increased sensitivity to platinum and longer survival in EOC patients with BRCA mutation [70]. This BRCA ness of ovarian cancer cells is also the reason for their response to PARP inhibitors which inhibits DNA repair [71]. Antiangiogenic agents also play a key role [72]. Greater understanding of tumor biology would help in better selection of drugs.

Chemotherapy

Among the chemotherapeutic drugs, carboplatin and paclitaxel continue to form the backbone and will be discussed in detail.

Carboplatin. Carboplatin and cisplatin are platinum compounds which act by causing DNA adducts. They have equal efficacy in ovarian cancer; however, carboplatin is preferred due to ease of administration and less emetogenicity and nephrotoxicity [73]. It is important to note that unlike many chemotherapeutic drugs, platinum is not a substrate for multidrug resistance protein (MDR1), which causes drug efflux out of the cell [74]. Another unique feature of carboplatin is the delayed hypersensitivity which generally occurs after a median of 8 cycles in about one-third of patients [75]. This is because there is exposure to low levels of free platinum in each cycle which causes sensitization and subsequent retreatment leads to a type I hypersensitivity reaction [75, 76]. Thus, one should be alert to this possibility with repeated platinum use and inform patients regarding its symptoms [76]. In those with mild reaction carboplatin may be continued with anti-allergic medications those with more severe reaction need discontinuation of carboplatin [77]. Though there are desensitization protocols [78], their use in routine clinical practice is difficult. Cisplatin may be used in those with carboplatin hypersensitivity with close monitoring [77]. In life-threatening reactions, however, no platinum should be re-challenged [76]. Use with liposomal doxorubicin reduces the incidence of hypersensitivity reaction possibly because of masking of antigenic sites by pegylation [79]. Although prolonged infusions have been associated with less hypersensitivity [76], prophylactic prolonged infusions have not shown to reduce the incidence in randomized trials with use of premedication [80].

Carboplatin is excreted almost completely by the kidneys [81]. The dosing is thus based on the area under the curve (AUC) of plasma concentration versus time which in turn depends on the renal clearance of the drug and thus affected by the glomerular filtration rate (GFR) [82]. This is done by using the Calvert formula, total dose in mg = AUC × (GFR +25) where 25 is a constant to account for the nonrenal clearance of the tissue bound carboplatin [82, 83]. Creatinine clearance is taken as a surrogate for GFR and is usually calculated by the Cockcroft-Gault formula [84]. However, it is important to remember that serum creatinine is also affected by diet, body composition and tubular secretion [84]. Thus, this formula may overestimate or underestimate GFR in those at extremes of age and body surface area, low serum albumin [84]. Thus, the estimated creatinine clearance should be capped at 125 mL/min [85]. For those with very low serum creatinine especially in elderly and cachectic patients a minimum s creatinine of 0.7 should be used [85]. In patients with single kidney or underlying medical renal disease a measured GFR using DTPA GFR may be considered.

Paclitaxel. Paclitaxel is the other backbone of treatment of ovarian cancer. It was derived from the bark of the pacific Yew tree, Taxus Brevifolia, hence the name taxane [86]. Today, though, there is a total synthesis of this natural product with growing demand [86]. Paclitaxel stabilizes microtubule and thus prevents spindle formation during metaphase ultimately leading to cell death, another mechanism being multipolar division [86]. It is highly albumin bound (95%) and mainly cleared by hepatic metabolism by cytochrome P450 isozyme CYP2C and CYP3A, with less than 10% renal clearance [87]. Thus, care needs to be taken in patients with hypoalbuminemia and with concomitant inducers/inhibitors of CYP3A. Since it is not soluble in water, solvent cremaphor EL is used. This is the primary cause of hypersensitivity with paclitaxel. Cremaphor leaches di-2-ethylhexyl phthalate (DEHP) plasticizer from PVC (polyvinyl chloride) bottles [88]. Hence, non-PVC bottles (glass, polypropylene) along with an inline filter is needed. Premedication with H1 and H2 blockers, dexamethasone and chlorpheniramine reduces the incidence of hypersensitivity to less than 10% [89], although severe anaphylaxis may still occur in 2%–4%. It causes joint pains and myalgias and it is important to prescribe analgesics preemptively. It may rarely cause cardiac bradyarrhythmia [89]. Apart from myelosuppression and alopecia, the other unique side effect is peripheral neuropathy which typically is the glove and stocking type. This is caused by axonal degeneration and demyelination and is contributed by both paclitaxel and cremaphor. It is dependent on dose and duration of infusion. Incidence of grade II-IV neuropathy is around 18% with 3 weekly paclitaxel and 26% with weekly paclitaxel [90]. Importantly, around half of survivors continue to experience some neuropathic symptoms [91].

The doublet of paclitaxel and carboplatin is usually given 3 times weekly. Paclitaxel is given before carboplatin. This is because in early pharmacokinetic studies it has been shown that there is 25% reduced clearance of paclitaxel if cisplatin is given before paclitaxel [92]. The hypothesis that a weekly dose dense regimen would improve survival was not proven to be true (ICON 8, Mito 7) except in one study (JGOG 3016) [93–95]. Weekly regimens are also associated with more myelosuppression [93]. Thus, the 3 times weekly regimen continues to remain the standard of care.

Antiangiogenic Agents

Angiogenesis plays a critical role in the development and spread of ovarian cancer [72]. VEGF expression leads to leaky peritoneal vessel and ascites [72]. Bevacizumab a humanized monoclonal antibody against VEGF has a therapeutic role in ovarian cancers. The main side effects being hypertension, proteinuria, thromboembolic events, bowel perforation especially in those who have received more than three lines of therapy, have bowel wall involvement or obstruction [96]. Thus, a careful work-up and patient selection needs to be done before initiating bevacizumab.

PARP Inhibitors

PARP (poly adenosine diphosphate [ADP]–ribose polymerase) repairs DNA damage by base excision repair. In cells which have a defect in the homologous repair pathway like BRCA, PARP inhibition would lead to cell death by "synthetic lethality" as both DNA repair mechanisms would be defunct [71]. Several different PARP inhibitors like olaparib, niraparib, and rucaparib are available. The main side effects of these are myelosuppression, fatigue, gastrointestinal, especially nausea, diarrhea, dyspepsia, raised creatinine (olaparib, rucaparib), transaminitis (rucaparib), and hypertension (niraparib) and rare side effects (occurring in less than 2%) like myelodysplastic syndrome and pneumonitis [97]. Platinum sensitivity is a marker for PARP sensitivity [98]. There can be reversion of germline BRCA 1 and 2 alleles leading to resistance to PARP inhibitors [46] and have thus provided a significant addition in the armamentarium of ovarian cancer.

Immunotherapy

Unlike other cancers immunotherapy is yet to find a place in ovarian cancer. Recent trials in recurrent ovarian cancer with high PDL1 expression, CPS score (combined positive score calculated by the percentage of PDL1 positive cells, tumor cells, lymphocytes and macrophages to total viable tumor cells) greater than 10% have shown to have response rates of 18%, PFS of 2 months and OS of 24 months even in patients who have received 3–5 lines of prior therapy with a platinum-free interval of more than 3 months [99]. More needs to be explored in this direction.

6.3.2 Early-Stage Ovarian Cancer

In early-stage ovarian cancer, it is important to determine the indication for adjuvant chemotherapy, number of cycles, and whether to use a doublet or a single agent. Patients with stage IA or IB low-grade ovarian cancers can be observed after surgery alone. The high-risk early stage, IA/ B high grade, I C, II all grades, and clear cell carcinoma any stage would benefit from adjuvant chemotherapy [100]. The five-year overall survival is improved from 65% to 76% with the addition of adjuvant chemotherapy (ACTION/ICON 1trials)

[100]. Around 60% of these patients had received single-agent platinum [100]. When using a doublet with paclitaxel and carboplatin, there was no difference in overall survival with use of three or six cycles (GOG 157) [101]; however, subgroup analysis showed a benefit in those with serous histology [102]. Thus, in most early-stage ovarian cancers who need adjuvant chemotherapy, six cycles of single-agent carboplatin alone can be considered, though three or six cycles of paclitaxel and carboplatin are also options. In those with high-grade serous cancers, six cycles of paclitaxel and carboplatin should be considered.

6.3.3 Advanced Stage Ovarian Cancer

In advanced stage ovarian cancers, six cycles of paclitaxel and carboplatin remain the standard of care. This can be given either as six cycles of adjuvant or three cycles of neoadjuvant chemotherapy (NACT) followed by interval debulking surgery and three cycles of adjuvant chemotherapy. Long-term pooled analysis of the EORTC and CHORUS trials have proven the noninferiority of NACT compared to primary debulking surgery (PDS) with reduced perioperative morbidity in the NACT arm [67]. In stage IIIC disease, the median PFS of 12 months and OS of 30 months is similar in both the arms [67]. A subset of these patients with extra pelvic disease less than 5 cm had improved PFS (27 vs. 17 months) and OS (47 vs. 39 months) with upfront PDS [67]. In those with stage IV disease, the use of NACT has improved the median PFS (10.6 vs. 9.7 months) and OS (24 vs. 21 months) [67]. It is interesting to note that unlike other solid tumors, in patients with ovarian cancers with pleural effusion, which is a stage IV disease, interval debulking surgery is still done if there is a response to chemotherapy. Paclitaxel and carboplatin are the standard chemotherapy; however, single-agent carboplatin can also be considered, especially in those with poor performance status, low albumin, and elderly patients. Once the performance status and albumin improve, paclitaxel can be added. Docetaxel or liposomal doxorubicin with carboplatin are other options, especially in situations where paclitaxel cannot be used because of either hypersensitivity reaction or underlying neuropathy.

It is important to bear in mind that Krukenberg tumor or tuberculosis may at times mimic advanced ovarian cancer. Hence, a thorough history, clinical examination including breast examination, evaluation of supraclavicular lymph nodes needs to be done. Tumor marker ratio of CA125 to CEA should be greater than 25 [25] and there must be at least a cytological diagnosis. Those with a ratio of less than 25 or odd features like bilateral solid ovarian masses should undergo a biopsy and GI endoscopy. A histopathological diagnosis (image guided biopsy) would help to better delineate the subtype such as low-grade cancers which have low response to chemotherapy [103] and would benefit from upfront surgery and rule out Krukenberg. There is a change in diagnosis in about 3% of patients [25]. Initial response to chemotherapy is seen in 60–80% patients [3]. In those patients who do not have a response to NACT, it is again important to do a biopsy to know the histopathology (low grade, Krukenberg) before considering them as platinum refractory. There are presently no standard guidelines on management of patients with no or poor response to NACT. Change of chemotherapy may be considered (e.g., to liposomal doxorubicin) [104]. Around 70% of them would eventually relapse and the 5-year overall survival is 30% [1]. The possibility of cure in advanced ovarian cancer thus remains unlikely as of date but remains a distant dream.

Several attempts have been made to improve upon this survival. Among chemotherapy, the addition of a third drug has not improved survival [105]. The use of weekly schedule also did not show an improved survival despite initial promise [93, 95]. Two approaches which have shown promise are the use of intraperitoneal chemotherapy and maintenance therapy with bevacizumab or PARP inhibitors.

Intraperitoneal Chemotherapy

Ovarian cancer has this unique feature of recurring repeatedly in the peritoneal cavity, which provides a sanctuary site [106]. Thus, the rationale of delivering chemotherapy into the peritoneal cavity where it would achieve a higher concentration, almost 20 times for cisplatin and 1000 times for paclitaxel, compared to plasma [106]. In patients with stage III ovarian cancer with residual disease less than 1 cm after primary cytoreductive surgery, intraperitoneal (IP) chemotherapy with cisplatin and paclitaxel compared to intravenous (IV) chemotherapy has shown improved overall survival from 51 to 62 months even after 10 years of follow up [106, 107]. However, because of toxicities such as catheter-related infection, higher incidence of myelosuppression, gastrointestinal toxicity and neuropathy only about 40% are able to complete all chemotherapy [107]. Thus, in spite of improved survival IP chemotherapy has not had a widespread acceptance. Also, the recent results of another randomized trial of IP versus IV chemotherapy where both arms received dose dense paclitaxel and bevacizumab did not show any significant difference in the two arms [108].

Hyperthermic Intraperitoneal Chemotherapy

The rationale for using hyperthermia in (HIPEC) is the increased penetration of chemotherapy with hyperthermia, formation of DNA adducts, protein denaturation, activation of heat shock protein which are receptors for natural killer cells leading to cytotoxicity [109]. HIPEC after IDS has shown an improvement in both PFS (14 vs. 11 months) and OS (46 vs. 34 months); however, no benefit in PFS or OS was seen when it was performed after primary cytoreduction [109, 110]. Thus, several questions about HIPEC still remain unanswered, and it is presently still not the standard of care in first line ovarian cancer as per the ESMO ESGO guidelines, while it can be an option in patients undergoing IDS as per NCCN [3, 111–113]. Thus, the debate continues. Proper patient selection with respect to both surgical and medical fitness to receive the intraperitoneal cisplatin needs to be considered. It will be important in the future to identify subgroups who might benefit from HIPEC [111].

Maintenance Strategies

As most advanced ovarian cancers relapse, it was thought that maintenance therapy may help prevent a relapse. One of the first drugs to be used was paclitaxel (175 mg/m^2 q 28 days) rationale being the killing of slowly growing cells in the cell cycle and its anti-angiogenic effect [114]. Though in a randomized phase III study 12 months of maintenance compared to 3 months did improve PFS (28 vs. 21 months), residual neuropathy was significantly more (23% vs 13%) [114]. Thus, maintenance paclitaxel is not routinely used. Subsequently, bevacizumab and now PARP inhibitors have been used as maintenance and have shown improvement in PFS.

Bevacizumab. Two large, randomized trials of maintenance bevacizumab, the ICON 7 and GOG 218 proved a PFS benefit of its use in patients with advanced ovarian cancer [115, 116]. In the GOG 218 in patients with stage III and IV epithelial ovarian cancer, bevacizumab was added in the adjuvant setting with standard chemotherapy with six cycles of paclitaxel and carboplatin, starting from cycle 2 and continued until cycle 22 at 15 mg/kg [115]. Compared to the control arm of no bevacizumab, an improvement in PFS was seen (14 vs. 10 months) but no improvement in overall survival [115]. Another arm in which bevacizumab was used only during chemotherapy did not show any benefit in PFS or OS. In the ICON 7, bevacizumab at dose of 7.5 mg/kg was given with adjuvant chemotherapy for 5–6 cycles and continued for another 12 cycles in patients with high-risk early stage and advanced epithelial ovarian cancer [116]. In the overall population compared to the control arm of no bevacizumab though an initial PFS benefit was seen (19 vs. 17.3 months), this was not statistically significant on longer follow up and there was no OS benefit [117]. Only in the high-risk subgroup (stage IV disease, stage III disease with suboptimal cytoreduction or inoperable) disease was a benefit seen in PFS (16 vs 10.5 months) and OS (39.7 versus 30.3 months) with bevacizumab in the long-term follow-up [117]. Also, it is associated with increased toxicity of hypertension grade II or higher in 18%–23%, thromboembolic events 7% and GI wall disruption seen in 2.8% [115, 116]. Bevacizumab is approved in the adjuvant setting. However, the magnitude of benefit, toxicity and costs needs to be weighed and discussed with the patient and may be considered in high-risk patients.

PARP Inhibitors. PARP inhibitors olaparib and niraparib have been approved as first-line maintenance therapy in advanced stage (FIGO III and IV) ovarian cancer [118, 119]. In the SOLO1 trial, patients with either germline or somatic BRCA 1 or 2 mutation, with stage III /IV high-grade serous, endometroid ovarian, fallopian tube of primary peritoneal cancer who have had a complete or partial response after platinum-based chemotherapy (they also underwent primary or interval debulking surgery) were randomized to receive either olaparib tablets 300 mg twice a day or placebo until disease progression [118]. This led to a PFS improvement of 36 months (49.9 vs. 13.8 months) [118]. Olaparib has also been used in combination with bevacizumab irrespective of BRCA mutation with a PFS benefit [120]. Niraparib maintenance in the first line was given in those with advanced ovarian cancer after response to platinum-based therapy, irrespective of BRCA mutation status. Niraparib was given at a dose of 300 mg (200 mg for those less than 77 kg/platelet count <150,000/mm^3) once daily for 36 months or disease progression. An HRD test (homologous recombinant deficiency) was done in all patients and was defined as a score of more than 42 or presence of BRCA deleterious mutation [119]. A benefit in PFS was seen in all patients (13.8 vs. 8.2 months) though the magnitude of benefit was more in those with HRD deficiency (21.9 vs. 10.4 months) [119]. PARP inhibitors are associated with toxicity mainly myelosuppression with anemia grade III or higher seen in almost 25% of patients apart from fatigue (70%), nausea (any grade 60%), myelodysplastic syndrome (1%), and pneumonitis (2%) [118, 119]. Other PARP inhibitors like Veliparib have also shown a PFS benefit when used as maintenance in first line irrespective of BRCA status and response to platinum [121].

Presently, the overall survival data is awaited with use of maintenance PARP in first line setting. It is approved for use in first line setting. Caution, however, needs to be exercised while awaiting OS data as some rare but serious complications like AML and pneumonitis have been observed apart from other toxicities like fatigue, nausea, and myelosuppression. The sequence of PARP inhibitor use is yet to be determined and whether to use it in first line maintenance or after relapse in a platinum-sensitive setting is yet to be determined.

Maintenance Strategy -which One?

In advanced stage ovarian cancer, the question of whether to observe or use maintenance and if so which one, should probably be determined by BRCA mutation/HRD deficiency status and high-risk features. Those with BRCA mutation/HRD deficiency could be offered maintenance therapy with PARP inhibitors. Those without mutation or HRD deficiency and with stage IV disease or inoperable or sub optimally reduced stage III disease could be offered bevacizumab.

Those without BRCA mutation and high-risk features can be observed. These targeted therapies are associated with high cost and toxicity with marginal PFS benefit and the cost benefit ratio should be discussed with the patient. Observation alone is also an option even in high-risk patients or those with BRCA mutation. Observation after paclitaxel and carboplatin-based regimen is the most common strategy presently used at our institute.

Hormonal Maintenance in Low-Grade Serous Carcinomas

Low-grade serous carcinomas are not as chemo responsive as high grade (23% vs. 80%) [122]. They have a higher expression of hormone receptor (58% vs. 27%) [123]. Thus, several studies have looked at the role of hormonal therapy in low-grade cancers, though there are no randomized trials to date in view of the rarity of the tumor. In a large retrospective review of maintenance hormonal therapy in stage II-IV low-grade serous ovarian cancers, significant improvement in PFS was seen (64.9 vs. 26.4 months) [103], there was however no improvement in OS. The hormonal therapy used was mostly either aromatase inhibitor or tamoxifen [103]. Thus, hormonal maintenance therapy could be considered in stage II-IV low-grade serous ovarian cancer after completion of standard platinum-based chemotherapy.

6.3.4 Follow-up

The follow-up of ovarian cancer patients is usually once every 3–4 months for 2 years and then every 6 months for the next 3 years, then yearly or earlier at any time if symptomatic [3]. At each visit, a detailed history especially with respect to increasing dyspepsia, bloating, increasing constipation, or laxative use and clinical examination including pelvic examination needs to be done. CA 125 on follow-up visits is commonly done if baseline CA 125 is high, ultrasonography of abdomen and pelvis on follow-up may done if the CA 125 is normal at baseline or patient symptomatic. Though treating based only on rising CA125 has not been shown to improve survival [124], monitoring with CA 125 may help to understand the disease kinetics and to decide on imaging. Imaging in asymptomatic patients is not routinely indicated. If patient is symptomatic or there is a significant rise in CA125 imaging a contrast CT scan of abdomen and pelvis is usually done. It is important to note that miliary deposits in the peritoneum may not be picked up on a CT scan and should be kept in mind when assessing patients with very, high CA 125 with minimal or no abnormality on the CT scan. The decision whether to initiate treatment for recurrent disease is based on the composite of symptoms and clinical findings, extent of disease radiologically and CA125.

6.3.5 Recurrent Ovarian Cancer

Most advanced ovarian cancers will eventually recur. This relapsing remitting course with intermittent chemotherapy and progressively shorter duration of remission after each relapse makes it more like a chronic disease that is eventually fatal. The management of recurrent ovarian cancers is summarized in Table 5.

Recurrent Ovarian Cancer—To Treat or Not to Treat

The art of treating recurrent ovarian cancer is to find the right time to treat it so that it is not too early or too late. The goal is to let the patient have maximum chemotherapy-free interval without letting the disease progress to a stage which would lead to excess morbidity and mortality. The rise of CA 125 precedes clinical progression by around one and a half months on an average [125]. Thus, on follow-up, it is important to look at the patients' symptoms, clinical findings and CA125 (not only the absolute value but also the tempo of rise). If any of these are abnormal, then it is usually a trigger

Table 5 Management of recurrent ovarian cancer

Primary treatment	<6 months	6–12 months	>12 months	>24 months
	Platinum resistant	Platinum sensitive		
		Partial		
Response to platinum	X	30%	55%	75%
Platinum partner	X	– Liposomal doxorubicin – Gemcitabine – Paclitaxel	– Paclitaxel – Gemcitabine/liposomal doxorubicin	
Single-agent chemotherapy	– Liposomal Doxorubicin – Oral etoposide – Weekly paclitaxel – Gemcitabine	X	X	X
PARPi[a]	X[b]	√	√	√
Bevacizumab[a]	√	√	√	√
Palliative care	√			

[a] May be offered as maintenance—Discuss cost–benefit toxicity

[b] May be offered after > than 3 lines of therapy in patients with gBRCA mutation

to do an imaging with a contrast-enhanced CT scan of the abdomen and pelvis. If the patient is asymptomatic, the CA 125 is not extremely high (in hundreds rather than thousands), and the CT scan does not show any significant disease that is likely to cause obstruction, then the patient may be observed and followed up after 3–4 months with instructions for early follow-up if she is symptomatic. Thus, a rise of CA 125 alone should not trigger the need for chemotherapy as that has not shown to improve survival [124].

6.3.6 The Concept of Platinum Sensitivity

Platinum is the backbone of treatment of ovarian cancer and initial response to it is around 75% [104]. This is because platinum causes DNA adducts, which cannot be repaired when the cell is BRCA1 or 2 deficient or has homologous recombinant deficiency (around 50%) [45]. However, around 20% of the high-grade serous ovarian cancers have cyclin E1 overexpression (CCNE1), which is primarily responsible for resistant or refractory disease [46, 126]. Most ovarian cancers eventually relapse. The time from completion of primary platinum-based chemotherapy to disease progression is termed as the platinum-free interval [127]. Progression on treatment or within 1 month are called platinum refractory [126]. If they relapse within 6 months, they are termed platinum-resistant while beyond 6 months is platinum sensitive [126]. Those relapsing within 6–12 months are partial platinum sensitive. Of all patients receiving first-line paclitaxel and platinum, around 10% have platinum-resistant disease, 20% relapse within 6–12 months while 50% relapse between 12 and 24 months [128]. The response to re-challenge with platinum depends on the platinum-free interval. This is around 30% for those relapsing between 6 and 12 months, 55% for those relapsing between 12 and 24 months and 75% for those relapsing beyond 18 months [129]. It is important to understand that these definitions of platinum resistance and sensitivity are from an era when disease progression was diagnosed radiologically and or clinically rather than just based on serological relapse increasing CA 125 [127]. The clinical implication is that if a patient has only a serological relapse at 4 months but clinical progression after 8 months, she could still be re-challenged with a platinum-based doublet. Thus, how progression is defined needs to be specified. In patients with a platinum-sensitive relapse, use of a non-platinum agent has not shown to improve survival [130]. Hence, one of the key points in treating relapsed ovarian cancer is defining their platinum sensitivity (Table 5).

6.3.7 Platinum-Sensitive Relapse

Systemic Therapy

Chemotherapy. Patients with platinum-sensitive relapse are treated with a platinum-based doublet. This has shown to improve survival compared to single agent platinum in the ICON 4 study, where there was in improvement in response rates (54–66%), PFS from 9 to 12 months and OS from 24 to 29 months with addition of paclitaxel to platinum [131]. The platinum partner could also be gemcitabine [132] or liposomal doxorubicin [133]. Response rates and PFS are similar with use of platinum with any of the partners. However, liposomal doxorubicin compared to paclitaxel has shown an improvement PFS (11.3 vs. 9.4 months) including in the partial platinum-sensitive group (9.4 vs. 8.8 months), though the overall survival was same (33 vs. 30.7 months) [133–135]. Carboplatin hypersensitivity was less with liposomal doxorubicin (6 vs. 19%), while thrombocytopenia was less with paclitaxel (6% vs. 16%) [133]. The three platinum partners have different toxicity profiles, gemcitabine associated with hematological toxicities (grade III/IV-24%), liposomal doxorubicin with hand foot syndrome (12%) and paclitaxel with neuropathy (≥Grade II-20%) [132, 133]. Thus, patients with a platinum-sensitive relapse can be rechallenged with platinum in combination with either paclitaxel, liposomal doxorubicin, or gemcitabine.

Bevacizumab. The addition of bevacizumab to gemcitabine and carboplatin followed by bevacizumab until progression improved PFS from 8 to 12 months, though there was no difference in OS of 33 months in the updated analysis of the Oceans trial [136, 137].

PARP Inhibitors (PARPi). PARPi maintenance after response to platinum. PARP inhibitors (Olaparib, niraparib or rucaparib) may be offered as maintenance in patients with recurrent ovarian cancer who have received ≥2 prior lines of platinum-based chemotherapy (i.e., primary treatment with platinum and on relapse treated with platinum) and had a response to the last platinum therapy irrespective of the BRCA status [98, 138–140]. The treatment is continued until disease progression or toxicity [98]. They should not have received prior PARP inhibitors [98]. Three large, randomized phase III trials have been the basis for approval of PARP inhibitors in this setting (Niraparib- NOVA, Olaparib-SOLO2, Rucaparib-ARIEL 3) [138–140]. Although approved irrespective of BRCA status in this setting, the magnitude of benefit of PARP maintenance depends on whether patient has germline BRCA mutation (gBRCA mut). The median PFS in patients with gBRCA mut was 21 vs. 5.5 months, while in those with non-gBRCA mut, it was 9.3 vs. 3.9 months for PARP (niraparib) vs. placebo [138]. This should be taken into consideration when discussing regarding cost-benefit ratio of PARP. The use of maintenance PARP inhibitors has shown to improve OS (52 vs 37 months) in patients with germline BRCA mutation [141].

PARPi Monotherapy. In platinum-sensitive relapse, rechallenge with a platinum-based doublet remains the standard of care. However, in patients who have received multiple lines of platinum-based chemotherapy treating with further platinum may be difficult in view of hypersensitivity, toxicity, problems with venous access or patient's desire of oral therapy. Thus, patients with germline BRCA mutation who have platinum-sensitive relapse and have received (≥3) lines of platinum-based chemotherapy may be offered treatment with single agent PARP inhibitor (olaparib, niraparib or rucaparib) [142–144].

Secondary Cytoreduction

Secondary cytoreduction in relapsed ovarian cancer has a limited role in a select group of patients. The survival benefit of this approach is still debatable and proper patient selection is the key.

Patient selection for secondary cytoreduction was evaluated by the German/Swiss DESKTOP OVAR (the Descriptive Evaluation of perioperative Selection KriTeria for OPerability in recurrent OVARian cancer) trial group who developed AGO (Arbeitsgemeinschaft Gynakologische Onkologie) score for predicting operability in patients with recurrent disease. The parameters predictive of complete resection include a good performance status (Eastern Cooperative Oncology Group 0), no residual tumor after primary surgery or early stage at primary diagnosis (FIGO I/II) and absence of ascites in preoperative imaging (cut-off 500 mL) [61]. This score was evaluated prospectively in DESKTOP II trial and predicted 76% chances of complete cytoreduction if these criteria were fulfilled [145]. Subsequently, DESKTOP III, a phase III randomized, multicenter international trial evaluated the role of secondary cytoreductive surgery plus chemotherapy versus chemotherapy alone in platinum-sensitive recurrent ovarian cancer at first relapse with positive AGO score [146]. Most of the patients (75%) had a platinum-free interval (PFI) greater than 12 months. In the final analysis, 75% patients underwent complete resection. The median PFS was significantly greater for surgery versus not 18.4 and 14 months. The primary end point analysis also showed a significant benefit in overall survival (OS). The median OS was 53.7 months with surgery (60.7 months in those with complete resection) and 46.2 months without surgery. However, those who had incomplete resection did worse (median OS 28.8 months) compared to no surgery [146]. The other randomized trial GOG 213 trial compared the role of secondary cytoreduction followed by platinum-based combination chemotherapy with or without bevacizumab in platinum-sensitive, recurrent ovarian cancer [147]. In this trial, the median PFI was 20 months, the selection of patients for surgery was based on investigator discretion (not strictly AGO score) and 63% underwent complete resection. Around 84% received bevacizumab. In this trial, the median OS was not significantly different in the surgery (50.6 months) versus no surgery arm (64.7 months) [147]. The possible reasons for the difference in the results of the two trials could be because of the use of bevacizumab and patient selection criteria.

Thus, secondary cytoreduction may be considered in patients with platinum-sensitive recurrent ovarian cancers who have good performance status, long platinum-free interval, single site of recurrence, and no ascites who are likely to achieve complete resection.

6.3.8 Platinum Refractory and Resistant Relapse

In patients with platinum-resistant or refractory disease the goal of treatment is to achieve optimal palliation of symptoms. It is important to involve the palliative care team early even when planning for systemic therapy rather than involving them only for end-of-life care. Overall general condition of the patient needs to be assessed. The benefit in terms of survival of few added months should be weighed against toxicities, cost, repeated hospital visits, and quality of life. The patient and the family should be involved in shared decision making. Palliative care alone without further cancer-directed treatment may be considered especially in patients with poor general condition. It is important to reassure patients that they would be continued to be cared for and supported and offer hope of symptom palliation. Thus, irrespective of whether prolonging life is possible or not patients should be able to live a better, pain-free, and dignified life with their loved ones.

Systemic Therapy

Chemotherapy. Patients with platinum-resistant relapse are treated with a non-platinum agents like liposomal doxorubicin, oral etoposide, weekly paclitaxel, single-agent gemcitabine, and topotecan (which can cause significant myelosuppression) [3, 148–152]. The response rates of any of these agents are similar and varies from 10% to 15% and results in a median PFS of 3–5 months. The choice of chemotherapy would depend on previous treatments received, toxicity profile, and performance status of the patient.

Bevacizumab. In patients with platinum-resistant relapse, the addition of bevacizumab to chemotherapy (weekly paclitaxel or liposomal doxorubicin or topotecan) in the AURELIA trial improved overall response rate from 12% to 27%, median PFS from 3.4 to 6.7 months, and median OS from 13.3to 16.6 months. The risk of gastrointestinal perforation is around 2% [153]. It is thus important to carefully select patients and exclude any bowel involvement. Thus, bevacizumab is an option in these refractory patients, especially in those with rapidly filling ascites to achieve palliation.

PARP Inhibitors. Platinum resistance is a surrogate for PARP resistance and the response rate to single-agent PARP inhibitors is around 30% with a median PFS of around 5 months [154]. It is thus not recommended in platinum-resistant disease [98]. However, in patients with germline

BRCA mutations without prior PARP exposure, who have progressed after three lines of therapy, single-agent PARP inhibitor (olaparib or niraparib)is an option [143, 154].

Metronomic Chemotherapy. Metronomic scheduling of chemotherapy drugs refers to the chronic frequent administration of low-dose chemotherapy (much below their maximum tolerated dose) [155]. It has the advantage of low cost, relatively less toxicity with reasonable efficacy. It has the potential to alter tumor micro-environment in addition to achieving tumor cell kill [155]. Various drug combinations have been used in metronomic therapy. Commonly used combinations are oral cyclophosphamide, etoposide with tamoxifen, others have also used in combination with celecoxib (± pazopanib) [156, 157]. Combination of oral cyclophosphamide and pazopanib (oral angiogenesis inhibitor) also achieved meaningful PFS of 5.5 months in heavily pretreated patients [158].

Though randomized trials comparing metronomic chemotherapy to cytotoxic chemotherapy are awaited and more evidence needs to be generated, they could be an option in platinum-resistant patients where meaningful palliation may be achieved with oral therapy at low cost.

Immunotherapy

The role immunotherapy is still under investigation [99, 159, 160]. However recent data on its use in heavily pretreated patients after three to five lines of therapy showed a PFS of 2 months and an OS of 17 months (24 months in those with CPS ≥10) [99]. However, when compared to standard chemotherapy (gemcitabine or liposomal doxorubicin immunotherapy [nivolumab]), there was no benefit in PFS or OS, though in responding patients the duration of response was longer [160]. Thus, the role of immunotherapy needs to be further explored to identify whether any subsets benefit from it.

6.4 Radiotherapy

Although epithelial ovarian cancers are radiosensitive tumors, the role of radiotherapy is presently limited to the palliative setting in patients with recurrent disease. Ongoing research with newer radiotherapy techniques seeks to re-explore its role in adjuvant setting especially in clear cell carcinoma.

6.4.1 Palliative Radiation

Patients with recurrent epithelial ovarian cancers (EOC) who after standard treatments develop locoregional relapses refractory to further chemotherapy may be offered palliative radiotherapy [161, 162]. These are usually patients who have repeated pelvic recurrence without ascites. Recurrent pelvic mass with predominantly presenting symptoms of pelvic pain, vaginal mass with severe discharge and bleeding or pelvic / nodal mass causing obstructive hydronephrosis or deep vein thrombosis can be effectively palliated with radiation [162].

Also, patients presenting with painful bone metastasis or spinal cord compression, scalp or brain metastases can be offered palliative radiation to alleviate symptoms. Most common palliative radiation regimens include 20 Gy/5# or 30 Gy/10# or 6–10 Gy/1#.

6.4.2 Adjuvant/Consolidation Radiotherapy

Presently adjuvant radiotherapy is not indicated outside of a clinical trial. The success of adjuvant platinum-based chemotherapy has replaced the role of radiotherapy. This is especially so because the transperitoneal spread of ovarian cancers required whole abdomen radiotherapy (WAR), which despite potential benefit in progression-free and overall survival had significant toxicities (especially gastrointestinal) due to inadequate coverage of large target volume and poor sparing of organs at risk (OAR) due to poor technology [163, 164].

In past two decades, there have been significant advances in imaging and radiation technology (planning software and delivery) which are available for clinical use. Linear accelerator (LA) based intensity-modulated radiotherapy (IMRT), volumetric intensity modulated arc therapy (IMAT) and helical tomotherapy (HT) have shown potential to achieve uniform dose delivery to the target with significant sparing of normal tissues namely liver, kidneys and bone marrow [7, 165, 166]. There is emerging data on the use of adjuvant radiotherapy in nonserous epithelial ovarian cancer (like clear cell), especially in early-stage disease (IC, II) [7, 167]. Consideration for further research and improving outcome is warranted.

6.5 Palliative Care

Palliative care is an approach that improves quality of life of patients and their families suffering from advanced life limiting illnesses by assessing and managing the physical, psychological, social, and spiritual concerns. According to the World Health Organization, palliative care should begin at the diagnosis of such illness and continued throughout the continuum of the disease, through end of life and after the death of the patient in form of bereavement support for the family of the deceased. This has shown to have an improvement in quality of life, better patient and caregiver satisfaction with treatment and sometimes improve survival. Palliative care team comprises of doctors, nurses and social workers as core team members and psychologists, counselors, rehabilitation services, chaplains, pharmacists, dieticians, etc., as the extended team members.

Palliative care team can facilitate accurate information provision to the patient and caregivers, thus helping them clarify their preferences, concerns and goals of care. This plays a pivotal role in coordinating and facilitating the entire patient care plan, helping patients and families to make informed choices, and assisting shared decision-making process.

It is important to look after the social, practical and financial effects of cancer diagnosis and treatment on patients and their families, which is a part of comprehensive palliative care planning for them. Thus, helping them to find feasible solutions to such issues, which are often missed in medical care.

Symptoms presenting early in the course of disease may be both disease- and treatment-related. Pain and fatigue are the commonest symptoms reported throughout the illness. Other symptoms include bloating, ascites, breathlessness, nausea, vomiting, loss of appetite, indigestion, oedema, altered bowel habits, constipation, and urinary symptoms, tingling and numbness of hands and feet due to neuropathy and hair loss secondary to chemotherapy, etc. Palliative care team does a thorough assessment and evidence-based management of these symptoms, thus providing comfort to the patient. A study by Lowery et al. suggested that introducing palliative care early in course of platinum-resistant ovarian cancers, is more cost effective [168].

Malignant bowel obstruction (MBO) is one of the most common complications associated with advanced ovarian cancers. Other such conditions that may affect patients with ovarian cancers are malignant ascites, malignant pleural effusions, lymphedema, and renal failure secondary to hydronephrosis depending on the stage of illness. These symptoms can be very distressing for patient as well as the caregivers, causing effects on their physical, emotional and spiritual well-being. This leads to stress, anxiety, depression, spiritual and existential distress. These effects can cause poor tolerance to disease directed treatments and may also affect their compliance with the treatment. Palliative care referrals can help the patient and their caregivers to deal with the physical symptoms and emotional challenges faced during and post treatment, which is very vital.

6.5.1 Malignant Ascites/ Pleural Effusions

Malignant ascites can occur in almost one-third of patients with advanced ovarian cancers. Refractory ascites can cause severe discomfort, pain, anorexia, fatigue, and breathlessness in patients, impacting their quality of life. Recurrent paracentesis or indwelling peritoneal catheterization can be done for palliation of symptoms. This may lead to metabolic impairment and hypoalbuminemia. Good communication with patient and caregivers, prognostication, titrating risk vs benefit of management and clear goals of care, should be established well in advance. Similarly, thoracocentesis, indwelling pleural catheters and pleurodesis can be useful for intractable pleural effusion, along with physiotherapy.

6.5.2 Malignant Bowel Obstruction (MBO)

The tumor can cause mechanical bowel obstruction as well as ileus by peritoneal carcinomatosis, kinking the bowel loops, encasing the mesentery, and limiting the bowel motility. This can cause partial or complete bowel obstruction which can be at single or multiple sites.

Patients present with severe vomiting, obstipation, decreased appetite, or colicky abdominal pain. Examination reveals abdominal distension, tenderness and reduced or absent bowel sounds with or without ascites. Evaluation is usually with an erect radiograph of the abdomen (s/o multiple air fluid levels). A CECT of the abdomen may be needed to determine the level of obstruction.

It is important to consider the feasibility of palliative surgical management in form of diversion stoma or intestinal stenting (for single site colonic obstruction). The contraindications to surgery for malignant bowel obstruction include obstruction at multiple sites, intractable ascites, peritoneal carcinomatosis, and involvement of proximal ileum, duodenum, and stomach and previous laparotomy demonstrating diffuse metastatic disease. Palliative surgery for bowel obstruction in ovarian cancer is associated with perioperative mortality rate of 6%–32% and morbidity rate of 7%–44%, depending on type and setting of surgery [169]. The overall outcome of patient admitted with bowel obstruction is dismal with a median survival of approximately 3 months. Thus, surgery should be considered only in a select group of patients in whom meaningful palliation may be offered without significant morbidity.

Conservative measures and symptom management in the form of bowel rest by keeping the patient nil by mouth, maintaining hydration, nasogastric tube aspiration, analgesics, anti-emetics, and corticosteroids should be started immediately in all patients with MBO. The possibility of any disease-directed therapy should also be considered. If surgery or disease directed treatments are not feasible, symptom management should be continued to keep the patient comfortable and maintain good quality of life.

6.5.3 Symptom Management in MBO

In patients with refractory MBO, where the goal is palliation of symptoms only, it is important to prognosticate, look at performance status, goals of care, have ethical and shared decision-making process, limit investigations to minimal, prioritize comfort over aggressive management, consider relief of distress, and avoid futile interventions.

The pharmacological management of malignant bowel obstruction are detailed in Table 6 [170–177]. The optimal use of these various pharmacological measures is needed to achieve maximal palliation.

6.6 Pain

Pain in ovarian cancer patients can be caused by the primary disease, intestinal obstruction, metastases, ascites, peripheral neuropathy due to chemotherapy, lymphedema, etc. Detailed assessment including thorough history taking, assessment of "total pain," including psycho-socio-spiritual aspects, careful examination, and relevant investigations are needed to reach pain diagnosis. Pain management is guided by underlying pathological mechanisms. Multidisciplinary approach for pain management includes anticancer therapies wherever applicable, appropriate pharmacological management, psychological and rehabilitation measures, or interventional pain management in form of neurolytic blocks (Fig. 8).

Table 6 Pharmacological management of malignant bowel obstruction

Hydration	Maintain adequate hydration (1–2 L/day) by intravenous/subcutaneous route
Pain	Opioids can be considered for pain management (as per WHO analgesic ladder), route of administration can be changed to IV/SC or transdermal Hyoscine butylbromide can be added for colicky pain
Partial obstruction	Reduce bowel wall edema—steroids Stimulate gut motility—metoclopramide
Complete obstruction (if unresolvable)	Reduce intestinal secretions Treat nausea and vomiting Nil by mouth
Antiemetics [170]	Metoclopramide: 30–120 mg/24 h via s/c or IV infusion Haloperidol: 2.5–5 mg/24 h via s/c or IV infusion
Anticholinergics [171]	Hyoscine butylbromide: 40–100 mg/day/SC or IV (not to be combined with pro-kinetics like metoclopramide)
Corticosteroids [172, 173]	Dexamethasone 6–16 mg/day/IV (to be given before 2 PM, given for 3–5 days as trial) If vomiting subsides, continue oral steroids Steroids act by reducing peritumoral edema and gut wall edema. Antisecretory action by reducing salt and water secretion in the gut.
Somatostatin analogues [174–176]	Octreotide 300 mcg/day subcutaneous to reduce gut secretions
Nutrition and TPN [177]	Not recommended in MBO from advanced cancer which is irreversible May be considered in patients who are severely malnourished (BMI <18.5–22 kg/m^2 depending on age), in whom a surgery or any disease directed therapy is planned, and who cannot be given enteral feeds.

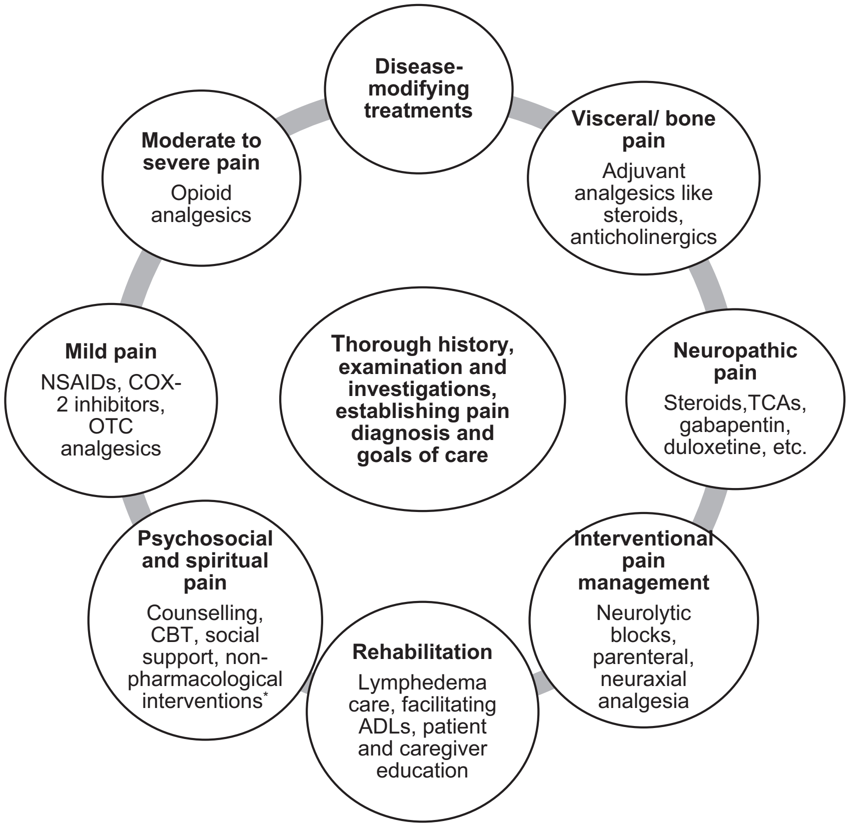

Disease-modifying treatments
Visceral/ bone pain
Adjuvant analgesics like steroids, anticholinergics
Neuropathic pain
Steroids,TCAs, gabapentin, duloxetine, etc.
Interventional pain management
Neurolytic blocks, parenteral, neuraxial analgesia
Rehabilitation
Lymphedema care, facilitating ADLs, patient and caregiver education
Psychosocial and spiritual pain
Counselling, CBT, social support, non-pharmacological interventions*
Mild pain
NSAIDs, COX-2 inhibitors, OTC analgesics
Moderate to severe pain
Opioid analgesics
Thorough history, examination and investigations, establishing pain diagnosis and goals of care

Fig. 8 Multidisciplinary management of total pain. *NSAIDs* Nonsteroidal anti-inflammatory drugs, *COX-2* Cyclooxygenase-2, *TCAs* Tricyclic antidepressants, *ADLs* Activities of daily living, *CBT* Cognitive behavior therapy

[a] Relaxation training, progressive muscle relaxation, hypnosis, distraction, guided imagery, yoga, acupuncture, music therapy, transcutaneous electrical nerve stimulation

Pharmacological management is based upon type of pain, somatic, visceral, or neuropathic and its severity. However, it is imperative to consider the patient's general condition, comorbidities, ongoing medications, compliance, response to previous treatment, history or risk for substance use disorders, or drug diversion, liver, and renal functions, understanding of symptom, caregiver support, affordability, psychological and social issues, possibility for follow up, etc. before deciding the pain management.

Thus, in patients where the goal is palliation of symptoms, it is important to limit investigations to minimal, consider relief of distress and prioritize comfort over aggressive management.

7 Conclusion

Ovarian cancers are a varied group of diseases which have perhaps little in common apart from the organ of origin. The ultimate goal of transition from a palliative to a potentially curative disease is yet to be reached for most epithelial ovarian cancers. While the endeavor to find newer treatments to improve survival continues, so must the care of the individual so that they can live longer and better.

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Non-Epithelial Ovarian Cancers

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1 Germ Cell Tumor

Malignant ovarian germ cell tumors comprise (MOGCT) 3–5% of all ovarian cancers [1]. The majority of the germ cell tumors are diagnosed at a young age (median age 16–20 years, range 6–40) and in early stage (60%–70%) [2–4]. They have a favorable prognosis, the 5-year overall survival ranging from 90% to 95% in early stage tumors to 60% to 80% for even advanced cancers [3]. After fertility-sparing surgery and adjuvant chemotherapy majority, 80% retain reproductive function [5]. Thus, these are potentially curable malignancy in young girls, and every effort should be made to provide adequate treatment and ensure treatment compliance and follow-up.

1.1 Presentation

Majority of malignant ovarian germ cell tumors present at young age, usually less than 40 years [3]. Usual presentation is with abdominal pain and distension. Around one-third may present with advanced stages with ascites and pleural effusion [6]. Around 10% present with acute abdomen. It is important to take menstrual history as some present with menstrual irregularity and also to look for secondary sexual development in a young girl. Those presenting with primary amenorrhea should undergo karyotyping to rule out dysgenetic gonads [5]. Thus, in germ cell tumors as in all other cancers, a careful history and clinical examination are mandatory.

1.2 Diagnosis

Characteristically germ cell tumor markers AFP, β hCG or S LDH are raised [1]. It is important to rule out germ cell tumor in any young patient less than 40 with suspected ovarian malignancy by doing tumor markers AFP, β hCG and S LDH. Also, CA 125 may be raised because of peritoneal irritation and a mistaken diagnosis of an epithelial ovarian cancer can be made if GCT tumor markers are not done.

Germ cell tumors are usually suspected on ultrasonography and a contrast-enhanced CT scan of thorax abdomen and pelvis is done at baseline for evaluation. Usually there is a unilateral ovarian mass; however, around 10% of dysgerminomas may be bilateral [5]. In those with advanced disease, it is important to look for tumor lysis syndrome [7]. For disease limited to ovaries, biopsy is not done because it will upstage the tumor and patients are taken up for exploratory laparotomy based on tumor marker and imaging findings. In those with advanced disease, biopsy is done, especially to rule out other diagnosis like lymphoma where only LDH may be high or other metastatic adenocarcinoma (Krukenberg) which may have low levels of AFP and β hCG [8]. In patients presenting with ascites and pleural effusion, it may sometimes be difficult to distinguish between adenocarcinoma and germ cell tumors on cytology alone, and a mistaken diagnosis of an epithelial ovarian carcinoma can be made if GCT tumor markers are not done. In patients with advanced disease who are extremely sick and tumor markers are high (usually in thousands) and radiology is suggestive of ovarian malignancy, chemotherapy may be initiated without a biopsy.

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1.3 Pathology

The WHO classification of germ cell tumors includes mature teratoma (dermoid) which are benign and most common and the malignant ovarian germ cell tumors which include dysgerminoma, yolk sac tumor, embryonal carcinoma, nongestational choriocarcinoma, immature teratoma and mixed germ cell tumor [1]. Apart from documenting the type of GCT, the presence of LVSI should also be noted [9]. In case of diagnostic dilemma, immunohistochemical markers may be used. Sal-like protein 4 is generally positive in all MOGCT. Dysgerminomas are positive for D240 and Alkaline phosphatase, placental type (PLAP) and OCT3/4. Yolk sac tumors are also positive for PLAP and glypican 3 [1]. Embryonal carcinomas are usually positive for Oct 3/4, CD30 and SOX2. There is an overlap of IHC markers, and thus, an IHC panel would help in diagnosis and characterization of the germ cell tumors [1, 9, 10].

1.4 Surgical Management

Given the early age of diagnosis and favorable outcome, every effort should be made to preserve fertility. The standard surgical procedure is unilateral salpingo-oophorectomy with preservation of normal adnexa and uterus with adequate staging which includes peritoneal washing, inspection, palpation and large biopsy of the omentum if normal, removal of adherent or abnormal omentum, inspection of the peritoneal surface and excision of any suspicious nodules, examination and palpation of retroperitoneal lymph nodes and sampling of firm or enlarged lymph nodes [1, 11, 12]. Random biopsies from normal looking contralateral ovary on inspection and palpation are not recommended; however, any suspicious lesion must be biopsied [1]. Suspicious lymph nodes should be removed but there is no evidence that complete pelvic and para-aortic lymphadenectomy is advantageous [1, 12]. Bilateral salpingo-oophorectomy should be done in those with dysgenetic gonads [13]. In postmenopausal patients with advanced disease or bilateral ovarian involvement, bilateral salpingo-oophorectomy and abdominal hysterectomy could be done with careful surgical staging [1]. Ovarian cystectomy alone is not recommended; however, in patients with bilateral ovarian involvement and who wish to preserve their fertility, contralateral cystectomy can be an option in selected patients [1, 5]. Fertility sparing management should be considered even in advanced disease due to chemosensitivity of tumor [1].

1.5 Chemotherapy

A landmark in the history of germ cell tumors was during 1977 when cisplatin-based chemotherapy was incorporated in the treatment of male germ cell tumors [14, 15] and which was soon incorporated to ovarian germ cell tumor [16] changing the prognosis of these tumors to highly curable malignancies. Today the standard chemotherapy regimen for GCT is bleomycin, etoposide and cisplatin (BEP) regimen [1]. This is a 5-day regimen with cisplatin and etoposide given on days 1–5 and bleomycin given on days 1, 8, and 15 every 21 days. Three to four cycles are given depending on the stage of disease [1]. One of the most important things to check before the initiating chemotherapy is the adequacy of renal function as the doses of all three drugs need to be modified based on renal function. Patients presenting with large retroperitoneal masses and obstructive uropathy may need percutaneous nephrostomy. Thus, while the BEP regimen has transformed the course of GCT from palliative to curative, the goal now is to reduce long-term toxicity while maintaining the high cure rates [12]. The Malignant Germ Cell Tumor International Consortium (MaGIC) is a collaborative effort toward that end [17].

1.5.1 Chemotherapeutic Drugs

Bleomycin

Bleomycin is an antitumor antibiotic which binds to and inhibits DNA synthesis. Less than 1% is bound to plasma proteins. It is mainly excreted by the kidneys (50%–70%) [18]. In view of low incidence of myelotoxicity [18], the dose of D8 and D15 bleomycin should not be withheld for low blood counts in the absence of any other toxicity. One of the most important and dreaded side effects of bleomycin is pulmonary toxicity (because of deficiency of bleomycin hydrolase in the pulmonary alveoli); the other common one is flagellate skin rash. Patients at high risk should be closely monitored for lung toxicity. High-risk features are age >40 years, creatine clearance <80 mL/ min, stage IV disease and cumulative dose >300 IU [18]. The incidence of significant pulmonary toxicity is around 6–10% with the 1% mortality [18, 19]. Pulmonary function tests have been done traditionally to monitor lung function. However, recently, it has been shown that though it does not correlate with subsequent toxicity and its role presently being questioned [19, 20]. What is most important is to monitor patients for cough, which has shown to correlate with toxicity [20]. Other symptoms being shortness of breath at rest or walking and chest tightness. New-onset symptoms especially cough should promptly trigger for doing an HRCT (high-resolution CT scan) of thorax [19, 20]. In case of new-onset symptoms and CT scan changes further bleomycin must be withheld. Chest infection needs to be ruled out. Pulmonary function tests and DLCO (diffusion lung capacity for carbon monoxide) may be helpful in patients with diagnostic dilemma and high-risk patients in addition to symptoms and CT scan [19]. However, bleomycin should not be withheld in asymptomatic patients without any CT chest findings only on the basis of PFT [19]. Having a symptom checklist, monitoring saturation before each dose of bleomycin and investigations based on above would be most important in avoiding bleomycin toxicity [19].

Etoposide

Etoposide is a topoisomerase II inhibitor. Its main side effect is significant myelosuppression. It is highly albumin bound and has renal clearance. It also needs dose modification in renal failure. Cumulative doses greater than 2000 mg/m^2 have been associated with acute myeloid leukemia which may develop 4–5 years after treatment [21, 22].

Cisplatin

Cisplatin acts by causing DNA adducts. Main side effects being that it is highly emetogenic and nephrotoxic. Other side effects being ototoxicity and neuropathy. Rarely, it has also been associated with thrombotic events [23]. It is important to closely monitor renal function and electrolytes during cisplatin use and use adequate hydration and antiemetics.

1.5.2 Adjuvant Chemotherapy

After surgery it is important to decide who is likely to benefit from adjuvant chemotherapy and who can be kept on active surveillance (Table 1). The FIGO (International Federation of Gynecology and Obstetrics) staging system is the same as that for nonepithelial ovarian cancer [1].

Whom Not to Give Chemotherapy—Surveillance

Patients with stage IA dysgerminoma and I A grade I immature teratoma can be kept under observation after adequate surgical staging [1]. It is important to keep them under active surveillance. Though around 80–85% stage IA dysgerminoma is cured by surgery alone, around 15% of patients relapse [1, 24, 25]. Though most of these relapses are sal-

Table 1 Adjuvant treatment of malignant ovarian germ cell tumor

Stage	Histology	Grade[a]	Management	Chemotherapy Number of cycles of BEP
Stage I				
A	Dysgerminoma		Active surveillance	
	Immature Teratoma	Grade I	Active surveillance	
		Grade II*	Consider active surveillance	
		Grade III*	Consider adjuvant chemotherapy	3
	Yolk sac tumor		Adjuvant chemotherapy preferred	3
B	Dysgerminoma*		Consider active surveillance	
	Immature teratoma*	Grade I*	Consider active surveillance	
		Grade II*	Consider active surveillance	
		Grade III*	Consider adjuvant chemotherapy	3
	Yolk sac tumor		Adjuvant chemotherapy preferred	3
C	Dysgerminoma[b]		Adjuvant chemotherapy	3
	Immature teratoma[b]*	Grade I*	Consider active surveillance	
		Grade II*	Consider adjuvant chemotherapy	3
		Grade III*	Consider adjuvant chemotherapy	3
	Yolk sac tumor		Adjuvant chemotherapy	3
Stage II	All histology		Adjuvant chemotherapy	3
Stage III	All histology		Adjuvant chemotherapy (may consider neoadjuvant chemotherapy)	3–4[c] (may omit bleomycin in cycle 4)
Stage IV	All histology		Adjuvant chemotherapy (may consider neoadjuvant chemotherapy)	4 (may omit bleomycin in cycle 4)

NOTE: *These are situations where adjuvant chemotherapy and active surveillance are both options, and the risk–benefit ratio should be discussed with the patient. When active surveillance is considered, patients must be adequately staged, postop tumor markers must be normal, and patient should be reliable for follow-up

[a] In immature teratoma, accurate grading requires adequate sampling of the entire specimen. If the entire specimen not sampled treatment as per the higher grade should be considered

[b] IC1 is a special subset of IC where both adjuvant chemotherapy and surveillance are options

[c] Adapted from [1, 6, 9]

vageable and the overall survival is close to 95%, it is important to detect these relapses early [1, 3, 26]. Immature teratoma stage IA grade I have not reported relapses in most series [27, 28].

To Give or Not to Give—Surveillance an Option

In patients with dysgerminoma stage IB adjuvant treatment is controversial though in IC adjuvant chemotherapy is usually recommended [1, 9]. However, in patients who have been adequately surgically staged active, surveillance is an option in IB and IC dysgerminoma if postoperative tumor markers are normal [1, 24]. Although around 20% to 25% of these patients may recur, they can be salvaged [24]. Thus, when planning active surveillance in these patients, it is important to ensure that they have undergone adequate surgical staging and are compliant for active surveillance and follow-up.

In Immature teratoma stage I (other than IA grade I where only surveillance indicated) the role of adjuvant chemotherapy is debatable, and it is not completely understood whether adjuvant chemotherapy reduces the risk of relapse [29]. Surveillance is an option if adequately staged, postoperative tumor markers are normal and patient is compliant for follow-up [1, 28, 29]. The most important factor predicting relapse in stage I is the Norris grade based on degree of immaturity, presence and amount of neuroepithelial component [27]. It should be noted that for accurate grading the entire tumor must be adequately sampled [27]. Those with grade I tumor (Stage IB/C) may be kept under active surveillance as the relapse rate is extremely low. Those with stage I grade II, the risk of recurrence on observation alone is around 2–20% in different series, and hence, stage IA/B may be kept under surveillance, while those with IC may consider chemotherapy [1, 27]. However, in those with grade III immature teratoma (stage I A/B/C), the risk of recurrence is to 70% with observation alone in older series [27], though in more recent series with adequate surgical staging, the relapse rate is around 20–40% [1, 24], and adjuvant chemotherapy may be considered.

Another occasionally faced problem is when a patient has high preoperative tumor marker and grade I or II immature teratoma with post op tumor markers which are normal, in this situation especially in large tumors other components may not have been adequately sampled, adjuvant chemotherapy may be considered.

Whom to Give Adjuvant Chemotherapy?

Stage I tumors with histology like yolk sac tumor, mixed germ cell tumors (other than dysgerminoma and immature teratoma which are detailed above) are treated with adjuvant chemotherapy. Though in pediatric stage I yolk sac tumor there are studies of observation alone, almost 50% of them relapse within a median time of 2 months [30] and in adults yolk sac tumors are associated with worse survival [24]; hence, adjuvant chemotherapy is the preferred option [1]. Stages II, III and IV of all histology are treated with adjuvant chemotherapy [1, 9].

How Many Cycles of Chemotherapy?

For early stage disease (stage I where chemotherapy indicated and stage II), usually three cycles of BEP are given. In patients above 40 years of age, bleomycin should be avoided, and four cycles of EP may be used instead. There is an increasing attempt in stage I tumors to reduce the number of chemotherapy cycles from three to two [9], though more data in adults is awaited.

In patients with advanced stage disease stage III, three cycles of BEP in case of completely resected disease and four cycles in patients with macroscopic residual disease [31], while in patients stage IV disease four cycles of BEP is given. In patients receiving four cycles, bleomycin may be omitted in the fourth cycle to avoid pulmonary toxicity [1, 9]. In patients with advanced disease in whom bleomycin cannot be given, other chemotherapy options are ifosfamide, etoposide and cisplatin [9].

1.5.3 Neoadjuvant Chemotherapy

In patients with advanced stage with extensive intra-abdominal disease, poor performance status where upfront surgery is likely to result in increased morbidity or fertility sparing surgery may not be possible, neoadjuvant chemotherapy (NACT) followed by fertility sparing surgery can be undertaken [6, 32]. In view of high chemo-sensitivity of these tumors, extensive surgical procedures should be avoided [9]. A response assessment is usually done after 2 cycles with tumor markers and CT scan. NACT with 4 cycles of BEP resulted in 70% patients achieving a complete and 22% partial response, who were then able to undergo fertility sparing surgery [6]. The estimated 10-year disease-free survival with NACT was 87% [6]. In patients who are extremely sick, low-dose induction chemotherapy (3 days of Cisplatin 20 mg/m^2 and Etoposide 100 mg/m^2) instead of the routine 5 days, and regular BEP postponed to D15) may be used taking cue from male GCT [33]. In these patients it is important to monitor for tumor lysis syndrome. Thus, in patients with advanced disease and poor performance status, NACT is a valid treatment option.

1.6 Follow-Up

Most guidelines recommend two monthly follow-ups (monthly for those on active surveillance) with clinical examination and tumor markers and ultrasound abdomen and pelvis for the first 6 months and then 2–3 monthly in second and third year, 6 monthly in fourth and fifth year and then yearly; a chest X-ray 6 monthly is also recommended for 2 years [1, 9]. For those on active surveillance, a 6 monthly CT scan in the first year at least, and some recommend for 2 years [1, 9]. Patients should be carefully counseled to avoid pregnancy in the first 2 years post treatment because it enhances the maximum chance of recurrence [34].

However, as such an intensive follow-up is not routinely feasible, at our institute, we usually follow patients three monthly in the first 2 years and then 6 monthly until 5 years, with clinical examination, tumor markers and ultrasonography of abdomen and pelvis. A CECT scan of thorax, abdomen and pelvis is done if tumor markers are rising or abnormal findings on ultrasound or symptoms. On follow-up, it is common to find functional ovarian cysts in the opposite ovary, and it is important to be aware of them, especially if tumor markers are normal. These are usually simple cysts that disappear post menstruation. Thus, a short follow-up after month post menstruation resolves the diagnostic dilemma and avoids further investigation. Occasionally on follow-up when patients present with rising β hCG, it is important to rule out pregnancy. The involvement of the family and medical social workers is important to ensure a regular follow-up.

1.7 Reproductive Outcomes

After fertility-sparing surgery and adjuvant cisplatin-based chemotherapy, 80–90% of patients resume menstruation within a median time of 6 months post treatment completion and most within a year [35–37]. Premature ovarian failure is seen in only around 3% of patients [38]. The infertility rate is higher in those receiving four cycles of BEP (33%) compared to three cycles (17%) [36]. Among those desiring conception, 80–90% have successful fertility outcomes [35–38]. The obstetric complications and miscarriage were not different from general population [37–39]. MOGCT have favorable fertility outcomes and patients should be reassured regarding the same prior to starting treatment.

1.8 Recurrent Disease Management

There is no definite treatment strategy for recurrent MOGCT. It depends on patients' previous lines of therapy and mainly extrapolated from male germ cell tumors [9]. If they have relapsed after 4–6 weeks of treatment completion, they can be rechallenged with platinum-based protocol like TIP (paclitaxel, ifosfamide, cisplatin) or VbIP (vinblastine, ifosfamide cisplatin), etoposide, ifosfamide and cisplatin (VIP) [40–43]. Treatment options for those relapsing on treatment or within a month include gemcitabine and paclitaxel with or without oxaliplatin [31]. If on recurrence tumor markers are normal, then it is likely to be a growing teratoma in which case surgery would the treatment of choice [9]. The role of autologous stem cell transplant and the results of the TIGER study which is a randomized phase III trial comparing conventional-dose chemotherapy using paclitaxel, ifosfamide and cisplatin (TIP) with high-dose chemotherapy using mobilizing paclitaxel plus ifosfamide followed by high-dose carboplatin and etoposide (TI-CE) as first salvage treatment in relapsed or refractory germ cell tumors, are awaited in male germ cell tumors [44].

1.9 Late Effects of Treatment

As many patients with MOGCT will be long-term survivors, it is important to monitor for late effects. Most of the data is from long-term follow-up of testicular cancers [45, 46]. Late effects like hypertension, hypercholesterolemia, ischemic heart disease, metabolic syndrome, renal dysfunction and ototoxicity need to be monitored [45, 46]. Pulmonary toxicity can be caused primarily by bleomycin but also by cisplatin [45]. The risk of second malignancies though low (standardized incidence ratio 1.4–1.8 needs to be monitored) [45].

1.10 Survivorship—Cure and Care

As with childhood cancer survivors' adolescents and young adults after being cured of their cancer need to be monitored systematically and cared for late effects of treatment as well as educational and socio-economic rehabilitation [47, 48]. The ultimate goal being that after being cured of their cancer, they become "resilient and autonomous" individuals with "optimal health-related quality of life" and "accepted in society at the same level" as their peers [47, 48].

2 Sex Cord Stromal Tumors

Sex cord tumors are a heterogeneous group of neoplasms which comprise 3–5% of all ovarian malignancies [1, 9]. Many of them have endocrine manifestations. They occur over a wide range of age groups, though many occur in middle age and in postmenopausal age groups [1]. They generally present in early stages (60–90%) and are usually unilateral [1, 9]. Surgery forms the mainstay of treatment in early stages. The 5-year overall survival rates are 75–95% in stage I tumors, 55–75% in stage II and 22–55% in stage III and IV [1, 49]. They may have late recurrences [50]. Thus, stage and histological subtype and features are the most important prognostic markers for these rare ovarian tumors.

2.1 Pathology

Ovarian sex cord stromal tumors with malignant potential mainly comprise of granulosa cell tumors and Sertoli and Leydig cell tumors. The granulosa cell tumor can be juvenile or of the adult type. These are two distinct histological subtypes. They are associated with hyperestrogenic states [1, 49]. The histological characteristic of adult granulosa cell tumors is the presence of Call Exner bodies (rosette like structures with eosinophilic material). In case of diagnostic dilemma, a panel immunohistochemical markers like inhibin, calretinin and FOXl2 may be used [1, 49]. Somatic mutations in the FOXL2 found in adult granulosa cell tumors are its potential drivers [51].

Sertoli-Leydig cell tumors usually are associated with androgen secretion and clinical virilization in 70–85% of these patients [49]. Pathological evaluation includes grade, histological features like retiform pattern and the presence of heterologous elements (mucinous, glandular, skeletal muscle or cartilage), which confer a worse prognosis [9]. DICER 1 mutations which cause disruption in the biogenesis and disruption of micro RNA expression of several genes have been associated with several rare cancers including Sertoli-Leydig cell tumors especially moderate and poorly differentiated ones [9, 52, 53].

2.2 Prognostic Factors

Age younger than 40 years, tumor size greater than 10 cm, mitotic index 5 or more /10 high power field are associated with poor prognosis though the data on the same is conflicting [49].These features do not constitute an indication for adjuvant chemotherapy in the absence of other risk factors. Surgical staging appears to be an independent prognostic marker [54]. The FIGO staging system is the same as that for epithelial ovarian cancer [1]. Preoperative tumor rupture was the most significant risk factor for relapse [49, 55].

2.3 Presentation

Clinically, they present with abdominal pain, distension and sometimes with risk of torsion. Granulosa cell tumors, juvenile subtype is more common in the adolescents and young adults while the adult type is more common in the peri- and postmenopausal age groups [49]. They present with abnormal vaginal bleeding. Sertoli Leydig cell tumors occur in second and third decades and 70–85% have hirsutism and clinical virilization [1, 49]. A detailed family history of other neoplasms should also be taken in patients with Sertoli-Leydig cell tumors and genetic counseling may be considered.

2.4 Diagnosis

Usually, an ultrasonography is done at baseline. Evaluation includes a contrast CT scan of abdomen and pelvis or an MRI. The radiological appearances are heterogeneous. The granulosa cell tumors are characterized by multicystic masses with solid components. On MRI, the tumors have sponge-like appearance [56].

Tumor markers Inhibin B is raised in granulosa cell tumor though CA 125 may also be nonspecifically raised [57]. It is important to know that there may be variation of S Inhibin B in the menstrual cycle with lowest level in late luteal phase [58]. Hormonal levels of estrogen, dehydroepiandrosterone, testosterone, luteinizing hormone and follicle stimulating may be done depending on the signs and symptoms of excess hormone production [9]. Other tumor markers like AFP, β hCG and LDH may also be done to rule out germ cell tumors in young patients.

In adult patients with granulosa cell tumor in endometrial sampling is recommended as because of the hyper estrogenic state there is an association with endometrial cancer in 3–6% patients [57].

2.5 Surgery

The extent of surgery in patients with SCST depends on age, histological subtype and desire for fertility preservation. In young patients desirous of fertility with macroscopically in stage IA disease a fertility-sparing surgery with unilateral salpingo-oophorectomy and adequate surgical staging is considered safe. However, patients with greater than stage I disease and postmenopausal women undergo total abdominal hysterectomy with bilateral salpingo-oophorectomy and complete surgical staging. Complete surgical staging includes peritoneal cytology, inspection of peritoneal cavity and biopsy of any abnormal areas and infracolic omentectomy. Systematic lymph node dissection is not indicated unless they are suspicious [1, 9].

2.6 Role of Adjuvant Chemotherapy

2.6.1 Stage IA/B

Granulosa Cell Tumor (Adult or Juvenile)

May be followed up after surgery alone as the 5-year survival after surgery alone is close to 95%. Hence, adjuvant chemotherapy is not indicated [1, 50].

Sex Cord Stromal Tumors

In those with heterologous or poorly differentiated elements, adjuvant chemotherapy is indicated while others without these poor risk factors may be followed up after surgery [1, 9].

2.6.2 Stage IC

Granulosa Cell Tumor

Juvenile granulosa cell tumor adjuvant chemotherapy in stage IC is indicated, although in IC 1 active surveillance is an option [1].

Adult Granulosa Cell Tumor

Those with stage IC1 may be followed up after surgery [1, 54, 55]. Patients with stages IC2 and IC3 receive adjuvant chemotherapy especially if they also have high mitotic index [1, 49]. Active surveillance is an option in IC2 and C3 [1].

Sex Cord Stromal Tumors

Adjuvant chemotherapy is indicated in all stage IC [1, 9].

2.6.3 Stages II–IV

All patients should receive chemotherapy irrespective of histology [1]. In patients with stage IV disease chemotherapy would be given with palliative intent.

2.6.4 Chemotherapy

Three to four cycles of BEP is the standard treatment with bleomycin omitted in those above 40 years of age. Paclitaxel and carboplatin is another active combination, which is given for six cycles and can be used in adjuvant setting. GOG 264 trial is comparing the efficacy of both and results are awaited [1, 9].

2.7 Recurrent Disease

In patients with granulosa cell tumors especially those with late recurrences, re-surgery with maximum cytoreduction where feasible is indicated [1, 9, 55]. The chemotherapy regimens used in recurrent settings include paclitaxel/carboplatin, doxorubicin, paclitaxel, ifosfamide based regimens [1, 9, 49]. The recent randomized phase II trial has shown the benefit of weekly paclitaxel with a 6-month PFS of 70% and no additional benefit of bevacizumab [59]. Hormone therapy in recurrent settings includes aromatase inhibitors, leuprolide and tamoxifen. Hormone therapy like Megestrol and GNRH agonists can also be used in relapsing patients [1, 49]. The phase II PARAGON study evaluating the role of aromatase inhibitors in the metastatic setting has shown a clinical benefit rate of 80% at 3 months and a median PFS of 8.6 months [60].

2.8 Follow-Up

These tumors may recur late even up to 20 years later and thus the need for life-long follow-up [54]. Patients are usually followed up with clinical examination, ultrasonography and tumor markers where indicated every 3–4 monthly in the first 2 years and then 6 monthly in years 3–5 and then yearly. CT scan is done based on clinical indication [9].

3 Small Cell Carcinoma Ovary of the Hypercalcemic Type

This is a rare yet aggressive tumor with poor prognosis and as the name suggests is associated with hypercalcemia. Thus, the work-up for these patients in addition to a CT scan of abdomen and pelvis, CA 125, includes measurement of serum calcium and chromogranin A. Pathologically, the differential diagnosis is of small round cell tumor and immunohistochemistry for SMARCA4 if available may be useful as these are associated with loss of nuclear immunoreactivity [9].

In view of the aggressive nature of the tumor, surgery comprises of total abdominal hysterectomy and bilateral salpingo-oophorectomy with peritoneal staging and full pelvic and para-aortic lymphadenectomy even in early stage. In advanced stages, surgery may be done upfront or debulking surgery after three cycles of chemotherapy if complete removal of the peritoneal disease can be achieved. The chemotherapy regimen used is cisplatin and etoposide and six cycles are given [9].

Despite all treatment outcome for these tumors is poor and newer treatment avenues need to be explored.

4 Conclusion

Nonepithelial ovarian cancers are a diverse group of diseases. The transition from a palliative to a potentially curative cancer was achieved for germ cell tumors almost 50 years back, and that inflection point is yet to be reached for the other ovarian cancers. The endeavor thus is to improve survival while reducing late effects of cancer treatment.

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Bone Sarcomas

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Abbreviations

AJCC	American Joint Committee on Cancer
DTPA	Diethylenetriaminepentaacetic acid
HDMTX	High-dose methotrexate
IMRT	Intensity-modulated radiation therapy
PET	Positron emission tomography

1 Epidemiology and Pathogenesis

Being rare, bone sarcomas present unique challenges both in diagnosis and treatment. Osteosarcoma, Ewing's sarcoma and chondrosarcoma are the three most frequent primary bone sarcomas [1, 2].

Osteosarcoma is the most common primary bone cancer in children and adolescents. The incidence has two peaks, with an age-adjusted incidence of 4 per million in patients ≤25 years or ≥59 years of age, and ≤2 per million among those aged 25–59 years. The incidence of osteosarcoma peaks with onset of puberty, in boys reported at ages 15–19 years and in girls at ages 10–14 years [1, 3]. In a series of 853 patients from Tata Memorial Hospital, Mumbai, the mean age was 19 years (range 3–64 years) [4]. The pathogenesis includes a combination of genetic changes including abnormalities in RB gene and P53 genes. The most common syndromes associated are Rothmund–Thomson syndrome, Li–Fraumeni syndrome and Werner syndrome. The second incidence peak in the elderly (age ≥60 years) is associated with Paget's disease or postradiation sarcomas [5].

Ewing's sarcoma, another bone sarcoma seen in children and adolescents, is discussed in a separate chapter in this book.

Chondrosarcomas are rare, representing approximately 20% of primary musculoskeletal malignancies. Most patients are in the fifth decade or older. Patients with secondary chondrosarcomas from Ollier's disease or Maffucci's syndrome present earlier, usually in the third or fourth decade.

2 Diagnosis

Patients with bone sarcoma present with swelling or pain that may disturb sleep at night and occasionally results in a pathological fracture. Complete clinical diagnosis involves establishing histological diagnosis, mapping disease extent and assessing various treatment options. This includes a thorough history and physical examination, details of prior intervention and treatment, clinical examination, assessment of the involved region, regional lymph nodes (an uncommon site of metastases) and lungs (commonest site for metastases). This necessitates local imaging, biopsy and imaging for systemic staging.

2.1 Radiological Imaging of the Involved Bone

Plain radiographs in two planes (anteroposterior and lateral) covering the whole extent of the involved bone are advised as an initial evaluation. In addition, an MRI and in occasional cases a CT scan is recommended. The additional imaging helps demonstrate extent of disease, relationship to neurovascular structures and adjacent joints, delineate necrotic versus viable solid tumor that helps guide biopsy, evaluates for skip lesions (separate tumor nodules within the same bone) and helps estimate surgical margins and create a tentative plan for eventual surgical resection. Imaging is repeated presurgery (toward the end of neoadjuvant therapy) to assess therapeutic response, reconfirm surgical margins (which are planned based on imaging showing the maximum extent of disease) and evaluate reconstructive options.

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2.2 Biopsy

Biopsy is performed after completion of all local imaging. Placement of the biopsy site is critical as it can significantly impact limb salvage and reconstructive options [6]. Due diligence is needed to place it appropriately so as to take the shortest, safest route to source adequate viable tissue. It is best that biopsies be planned by the treating team or after an orthopedic oncology consult. A core needle biopsy is sufficient and standard of care in most cases. An open biopsy is required in a few cases after failure of yield or diagnosis after multiple well-targeted needle biopsies or if additional tissue is required for research or tumor repositories (after appropriate consent). For challenging anatomic locations or where a large component of the tumor is necrotic, image guidance (IITV imaging/CT scans/ultrasound) may be used to increase tumor yield [7, 8]. As a general rule, biopsies are performed away from sites of pathological fracture. Due care is necessary to avoid contamination of the adjacent joint, critical structures or multiple compartments. Often special cytogenetic or molecular oncology testing may be necessary to arrive at a diagnosis. Microbial cultures are sent when infection is suspected or is a differential diagnosis. Frozen section may be used to ascertain viability of tissue sent in cases with predominantly necrotic tumor [9]. Biopsy cores should be processed together. The material must not be divided with the intent of sending it to different laboratories. Due to the heterogeneous nature of sarcomas, separating tissue or cores lead to improper reports and avoidable confusion. Discrepancy is sorted by seeking second/subsequent opinions on the same material by sending slides and blocks for review. Fine-needle aspiration cytology is discouraged for diagnosing bone neoplasms as the rate of nondiagnostic or nonrepresentative sampling is high due to absence of matrix in the sample (FNAC yields cells not matrix). If an open biopsy is needed, meticulous hemostasis, use of drains and precautions to avoid a pathological fracture through the bony window viz., a small oval window, cement plugging, avoiding sharp corners etc. must be taken. Confirmation of diagnosis helps guide appropriate staging, the need for molecular genetic testing, baseline organ assessment and supportive care including fertility preservation in preparation for neoadjuvant therapy. A biopsy plays a vital role in diagnosis and has a bearing on definitive management and disease-specific-survival of the patient. It requires considerable thought and planning prior to its execution and adequate correlation of the clinical evaluation, imaging and histopathology in order to be of maximum benefit to the surgeon and the patient.

2.3 Staging

Staging is guided by the final histologic diagnosis toward evaluating the commonest metastatic sites. It helps map disease burden, communicate prognosis and decide intent of treatment. Multidisciplinary input is often required to plan the treatment course and consider options for clinical trial recruitment. Lungs are the commonest site for metastases in all bone sarcomas. A noncontrast thin section (1 mm or less) scan using high resolution helical CT is most sensitive and detects even small nodules [10]. Technetium radionuclide bone scanning is the recommended method to evaluate for osseous metastases and skip lesions [11]. A fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan though not the standard of care may be used and may add value in response assessment to neoadjuvant therapy and prognostication. The commonest staging systems used were developed by Enneking et al. and The American Joint Committee on Cancer (AJCC). The Enneking system characterizes tumors that have not metastasized based on their histological grade (low grade 1 vs. high grade 2). These are subdivided into A for tumors that are intramedullary and B for tumors that extend beyond the cortex. Stage 3 are tumors that have metastasized [12]. Though the AJCC classification has not been adopted widely by the sarcoma community, the updated 17th edition of AJCC has distinct groups for axial, appendicular skeleton, pelvis, facial bones and the skull [13]. While beneficial in comparing outcomes across institutes for different stages, it adds little value in individual patient prognostication and does not consider treatment variables that alter survival (response to chemotherapy, for instance).

3 Osteosarcoma

Osteosarcoma is defined as a primary malignant tumor in which the malignant mesenchymal cells produce osteoid and/or immature bone. There are often areas with chondroblastic or fibroblastic differentiation. Hematoxylin and eosin-stained specimens remain the gold standard for the histological diagnosis, but recently molecular signatures have assisted in diagnosing certain bone tumors (Table 1).

The World Health Organization classification of osteosarcoma includes: conventional, telangiectatic, small cell, low-grade central, secondary, parosteal, periosteal and high-grade surface variants [14].

3.1 Conventional High-Grade Osteosarcoma

It commonly occurs in the metaphyseal region around the knee, but may occur in any bone. It presents as a mixed lytic-sclerotic destructive lesion with a wide zone of transition and an aggressive periosteal reaction often with a sunburst pattern and presence of a Codman's triangle (Fig. 1). Vast majority of osteosarcomas show fluffy, amorphous cloudlike opacities within the lesion that characterize osteoid

Table 1 Molecular signatures and their clinical applications in osteosarcomas and chondrosarcomas

Tumor	Molecular abnormality	Differential diagnosis	Test method
Low-grade central osteosarcoma	Ring chromosomes with CDK4 and MDM2 amplification	Fibrous dysplasia, desmoplastic fibroma, fibrosarcoma	FISH, IHC, quantitative PCR
Parosteal osteosarcoma	Ring chromosomes with CDK4 and MDM2 amplification	Myositis ossificans, osteochondroma, bizarre parosteal osteochondromatous proliferation, fibrous dysplasia	FISH, IHC, quantitative PCR
Chondrosarcoma (CS)	Somatic IDH1 and IDH2 mutations present in 30%–90% of sporadic tumors. Mosaicism of post meiotic mutations in Maffucci's and Ollier's disease is seen in ~100%	Chondroblastic osteosarcoma, mesenchymal CS, chordoma (with soft tissue extension), periosteal/parosteal osteosarcoma	PCR-based methods
Dedifferentiated chondrosarcoma (CS)	Somatic IDH1 and IDH2 mutations originating from low-grade CS	Chondroblastic osteosarcoma, undifferentiated high-grade bone sarcoma, dedifferentiated chordoma	PCR-based methods
Mesenchymal chondrosarcoma (CS)	Rearrangement leading to HEY1-NCOA2 fusion transcripts	Chondroblastic osteosarcoma, dedifferentiated CS, Ewing's sarcoma	RT-PCR, FISH

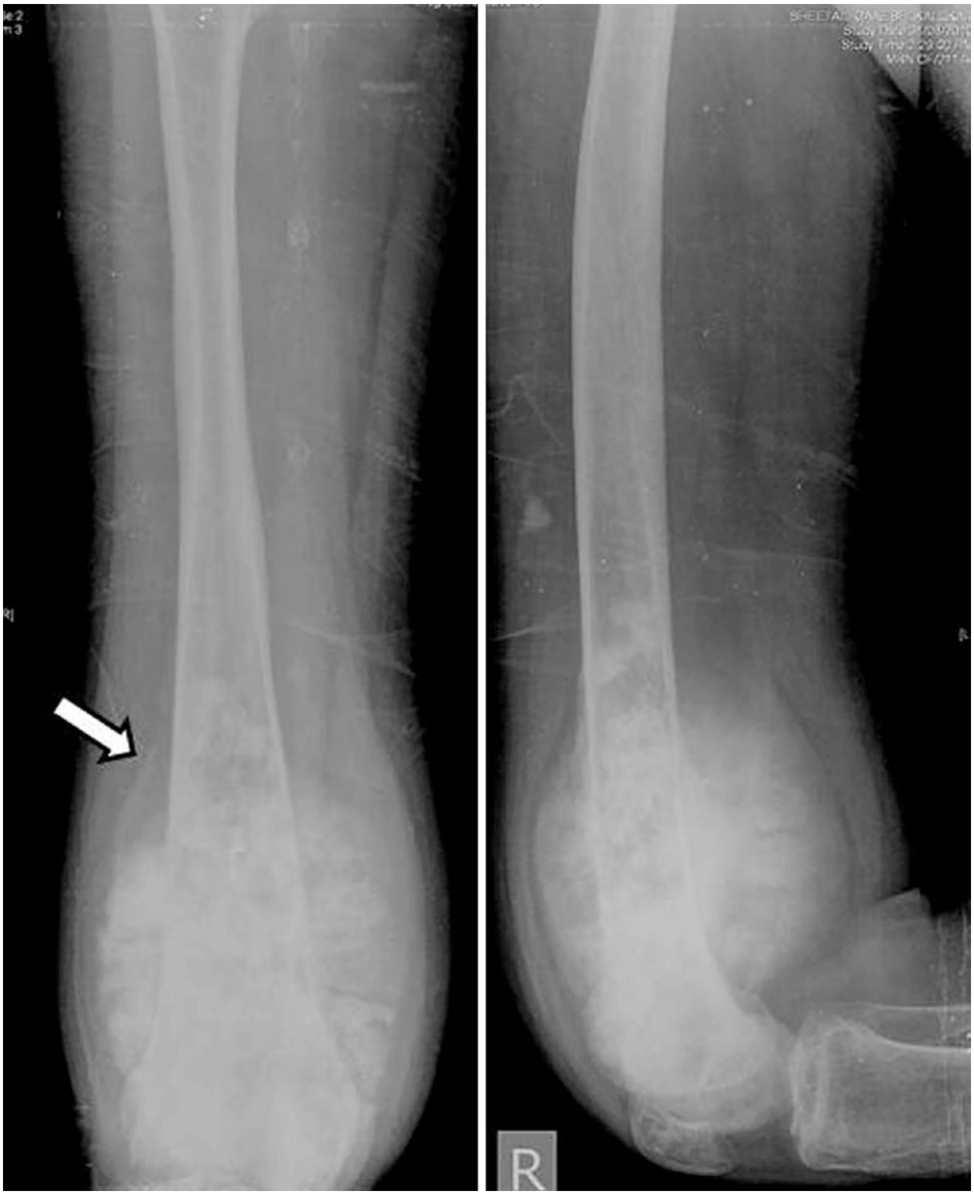

Fig. 1 Osteosarcoma. Radiograph of a high-grade conventional osteosarcoma of the distal femur showing a periosteal reaction with a Codman's triangle (arrow)

matrix alongside a large unmineralized soft tissue component [15].

3.2 Parosteal Osteosarcoma

It accounts for around 5% of osteosarcomas. It is commonly metaphyseal in location with the distal posterior femur being the most frequent site. It appears as a lobulated, exophytic mass, with dense ossification and a “stuck on” appearance adjacent to the cortex. A string sign which is a plane between tumor and adjacent normal cortex may be present in radiographs. Invasion into the medullary canal may occasionally be observed. It is predominantly low signal on both T1 and T2 MRI images (Fig. 2). Differential diagnoses include benign and malignant entities such as osteochondroma, myositis ossificans, periosteal chondroma, periosteal chondrosarcoma and other juxtacortical osteosarcomas [16].

3.3 Periosteal Osteosarcoma

This is the second most common juxtacortical osteosarcoma. It is usually seen in diaphyseal long bones. It is predominantly cartilaginous and is an intermediate- or high-grade tumor. It presents with a soft tissue mass and an irregular periosteal reaction associated with cortical thickening. Intramedullary invasion is documented but rare (Fig. 3). On MRI it has T2 hyperintense areas with small foci of T1 hypointense areas with calcified matrix. It is difficult to distinguish it from a high-grade surface osteosarcoma, the latter is more likely to include the whole circumference and invade the medulla.

3.4 High-Grade Surface Osteosarcoma

This is a rare variant and occurs in the same location as periosteal osteosarcoma with the femur being the commonest site. Imaging shows dense ossification, periosteal reaction and cortical erosion. Often circumferential thickening is seen and the rate of intramedullary invasion is commoner than in periosteal osteosarcoma. Differential diagnosis is similar to periosteal osteosarcoma.

3.5 Telangiectatic Osteosarcoma

This is an aggressive form of osteosarcoma, commonly occurring at metaphyseal sites in long bones, usually in the first two decades of life. It characteristically causes aggressive cortical destruction, expansion, a large soft tissue component and minimal sclerosis. MRI images show multiple fluid levels with hemorrhagic cystic components. Subtle osteoid may be visible on CT images. Enhancing nodular thick septa with presence of osteoid mineralization differentiate it from an aneurysmal bone cyst on MRI.

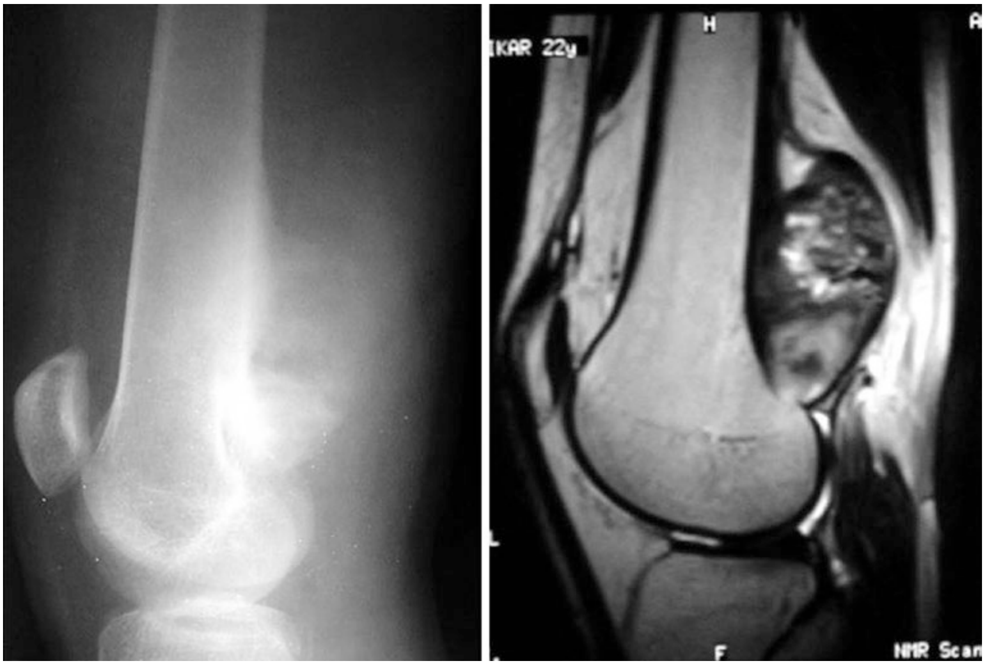

Fig. 2 Parosteal osteosarcoma. Radiograph and MR images depict a parosteal osteosarcoma of the posterior distal femur

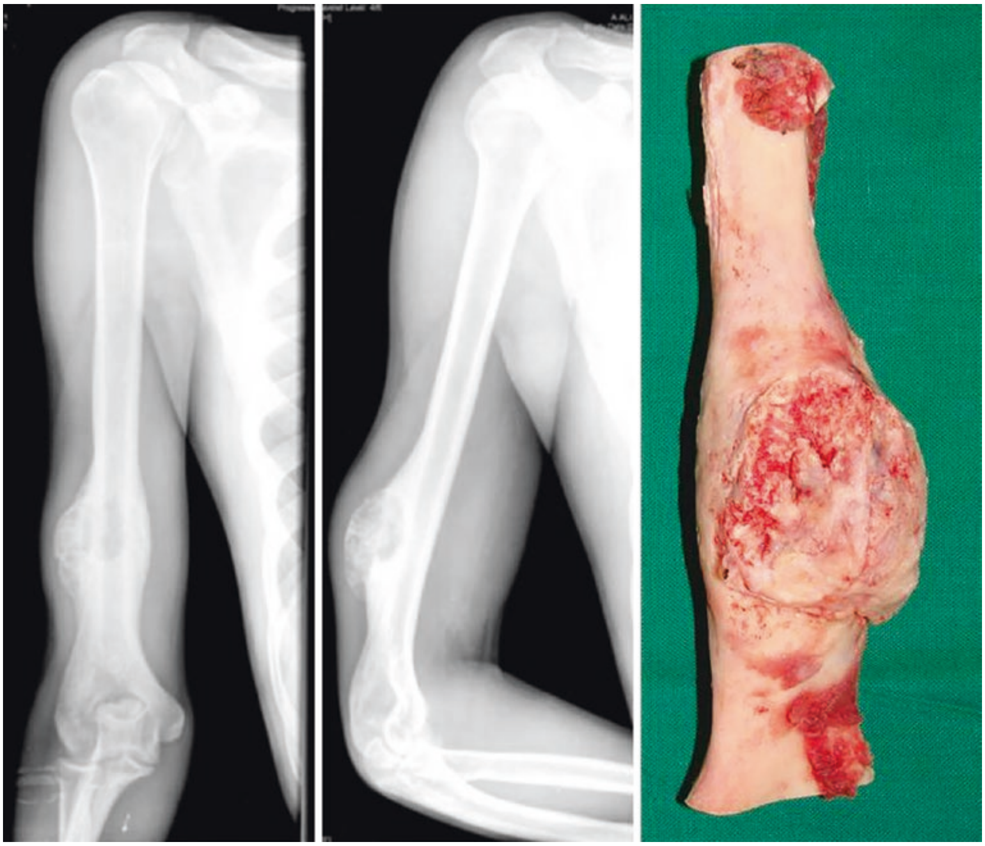

Fig. 3 Periosteal osteosarcoma. Radiograph of a periosteal osteosarcoma of the humerus with the histology specimen demonstrating a surface tumor

3.6 Small Cell Osteosarcoma

This is a rare variant of osteosarcoma. While morphology may mimic Ewing's sarcoma, presence of osteoid matrix and absence of EWS-ETS translocation help distinguish it from Ewing's sarcoma. Imaging features show permeation, lysis and cortical destruction often accompanied by a large soft tissue component. A differential diagnosis is lymphoma of bone which may also show permeative lysis with large soft tissue component but calcification is uncommon.

3.7 Low-Grade Central Osteosarcoma

This uncommon subtype of osteosarcoma occurs in the intramedullary location of femur or tibia. It has much better prognosis than conventional osteosarcoma and surgical resection is adequate. The radiograph shows an expansile lytic lesion with thick trabeculae or occasionally a dense sclerotic pattern. It commonly is associated with cortical disruption and soft tissue expansion. Benign fibro-osseous lesions which include fibrous dysplasia, nonossifying fibroma and desmoplastic fibroma are common radiological differentials.

4 Chondrosarcoma

Chondrosarcoma is a malignant tumor producing cartilaginous matrix and the primary variant is the third most common primary malignant tumor arising in bone. The subtypes include primary, secondary to osteochondroma, clear cell, juxtacortical, mesenchymal, dedifferentiated and extra skeletal.

On histopathology there is an increased variation in cell size and often bi nucleated cells. Mitotic figures are rare. Myxoid and cystic areas indicate malignancy. Lobular nests of cartilage with varying degrees of cellular atypia are common. As cellular atypia increases, the grade of the malignancy increases: Grade 1 chondrosarcoma is moderately cellular (vis-à-vis enchondroma) and shows mild nuclear atypia and bi-nucleation. Grade 2 chondrosarcoma is more cellular and shows more nuclear atypia. Grade 3 chondrosarcoma is very cellular and shows pleomorphic and anaplastic tumor cells which are mitotically active. Necrosis may be seen. Immunohistochemistry is positive for vimentin and protein S-100, but negative for cytokeratin and EMA.

4.1 Conventional Intramedullary Chondrosarcoma

It presents in the long tubular bones and flat bones, femur being the most common site. The innominate bone is affected in up to one fourth of the cases. Radiographs show a mixed lytic sclerotic pattern of mineralization, typical ring and arc chondroid matrix, deep endosteal scalloping (over two-thirds the bone thickness) and soft tissue extension (Fig. 4). The high water content leads to high T2 signal on MRI and low attenuation on CT images. Distinction of grade 1 chondrosarcoma and enchondroma is challenging on pathology alone. Imaging and clinical details are essential in attributing the correct grade for optimal therapy. FDG PET CT scan is currently being evaluated to help distinguish various grades of chondrosarcoma. Presence of a soft tissue extension precludes the diagnosis of a benign enchondroma. Enchondromas of the hand and feet may cause significant radiological endosteal scalloping while remaining benign [17].

4.2 Clear Cell Chondrosarcoma

This is a rare and slow growing variant affecting long tubular bones, most commonly the epimetaphyseal region of the femur and humerus. Radiographs show a predominantly lytic lesion, cartilaginous matrix is not as frequent. T2 weighted MRI images are heterogeneous with high signal intensity.

4.3 Juxtacortical Chondrosarcoma

These are also referred to as periosteal or parosteal chondrosarcoma. Radiographs show a dense mineralized lesion with erosions in the underlying cortex. Periosteal osteosarcoma is a close differential diagnosis due to its predominant cartilaginous matrix. The latter present in a younger population (10–25 years), are commonly diaphyseal and are associated with a hair on end periosteal reaction helping to distinguish it from juxtacortical chondrosarcoma.

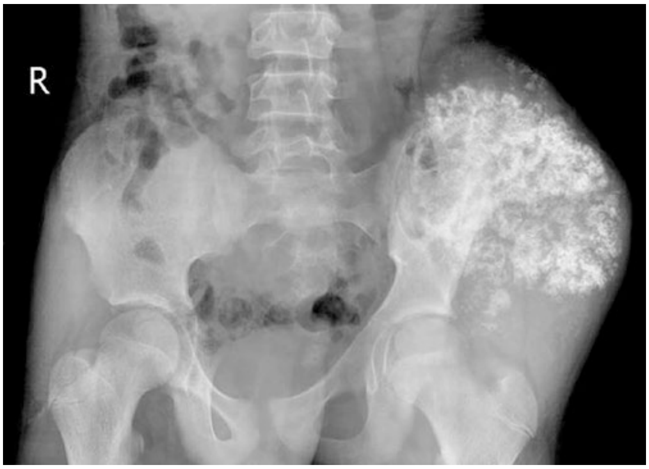

Fig. 4 Chondrosarcoma. Radiograph of a chondrosarcoma of the pelvis, a common site for a chondrosarcoma

4.4 Mesenchymal Chondrosarcoma

This is an aggressive variant with more propensity to metastasize. The axial skeleton is more commonly affected than the appendicular skeleton. Radiographs show destructive lesions with cortical permeation and soft tissue component. Cartilaginous matrix enhancement is heterogeneous and often lacks peripheral enhancement. Pathology often shows round cells similar to that seen in Ewing's sarcoma intermixed with a mesenchymal component.

4.5 Dedifferentiated Chondrosarcoma

This is a highly aggressive variant with very poor 5-year survival rates. Femur, pelvis and scapula are the commonest sites. Radiographs and other imaging findings are not specific. A large soft tissue component and decreased matrix mineralization are often seen.

5 Treatment

The patient outcomes in sarcomas are governed by an interplay of host, tumor and treatment strategies. The use of effective adjuvant modalities and appropriate function preserving surgery in a coordinated multimodality approach are of paramount importance. While multiagent chemotherapy and surgical excision is the standard of care in osteosarcoma, chondrosarcomas are largely treated with surgical excision alone.

6 Osteosarcoma

Chemotherapy is a vital component for the treatment of high-grade osteosarcoma and has increased survival substantially. Majority of the patients have micro metastasis at diagnosis and merit chemotherapy to optimize outcomes. A handful of chemotherapeutic agents are active in osteosarcoma, namely, doxorubicin, cisplatin, ifosfamide, high-dose methotrexate (HDMTX) and etoposide. However, it has been shown that the first three drugs have response rates from 26% to 43%, while etoposide had only 4% activity as a single agent.

6.1 Tumor Kinetic Principles and Cell Kill Models

Tumor comprises proliferative as well as dormant cells. Chemotherapeutic agents kill the proliferative pool, and doses and scheduling of drugs can significantly affect tumor lysis. Dose-intensity actually is defined by the drug delivery over a defined time and is derived by a formula as dose according to body-surface area mg/m^2 divided by chemotherapy completion time. This can be enhanced either by increasing drug dose or decreasing the total time to complete treatment. Various options are prevalent in practice to increase the dose-intensity with varied biologic and clinical implications Giving drug "A" at dose "B" 3 weekly results in dose intensity "value" of B/3 per week; doubling the dose yields an intensity of 2B/3; however, prolonging the cycle interval to 6 weeks yields an intensity of 2B/6 which equals a value of Y/3 and is lesser despite increasing the dose. Notably, an increased dose is not directly proportional to increased efficacy. Rather, there are several factors which determine the treatment effect inclusive of the respective cell kill from each chemotherapy dose and the overall treatment time(frequency of cycles) to deliver the cumulative chemotherapy dose and the pace of tumor repopulation interspersed between the chemotherapy cycles.

Another approach to increase the treatment effect is dose density, i.e., same dose intensity is maintained with the drug being delivered at shorter time intervals. This is found to be more effective due to the reduced incidence of tumor repopulation by surviving cells and the decreased possibility of development of drug resistant clones [18]. For example, if dose B is delivered biweekly, it will have a dose-intensity of B/2 which in turn would be similar to the doubled dose (dose 2B) if delivered once in every 4 weeks. The first strategy will still be superior with regard to dose density, and at the top of the dose–response curve, as the treatment interval is extremely important.

Similarly, sequential noncross-resistant chemotherapy cycles lead to higher cytotoxic effect as they are more dose dense. Notably, human solid tumors follow a Gompertzian growth pattern rather than log-kill model wherein the growth rate is inversely proportional to the size of tumor and hence decreases with increasing tumor size, up to a certain mass/volume and essentially plateaus there [19]. Likewise, tumors regrow fast post-suboptimal therapy, and hence, tumor eradication will not be achieved, which could have been the case in liquid malignancies which follow a simple log kill model. The log kill model was the first significant proliferation model described in oncology, which hypothesized that enough individual drug doses used in enough number of cycles would kill a significant percentage of tumor cells (if not all), and might cure cancer. This formed the basis of adjuvant chemotherapy regimens of the earliest generation. However, this has not been proven in all cancers, perhaps due to tumor heterogeneity with chemo sensitive cells interspersed with slowly growing resistant clones. To circumvent this issue, different permutation combinations of drugs are needed. Combinations could potentially affect efficacy due to dose modification of individual drugs. Chemotherapy cycles with alternating drugs (rather than sequential)("A" then "B" then "A" and so on) lengthen the interval between drug delivery and hence is potentially detrimental. This hypothesis was proposed by Norton and Simon that treatment should be first directed toward the dominant, rapidly proliferating cells and then toward the dormant, slowly growing resistant cells. This sequential pattern of therapy (wherein every "A" would be delivered first and then every "B" followed—i.e., AAAABBBBB), is inherently more dose-dense and was demonstrated superiority in various tumor types.

A meta-analysis demonstrated an improved survival in a multidrug regimen with three drugs in comparison to two drugs; additionally, it also noted that four drug regimen was not only not superior to three drugs rather was found to be more toxic [20]. The Cochrane review suggest inadequate evidence for or against HDMTX-based or non-HDMTX regimens (Table 2) [14, 15]. International guideline suggest toward using HDMTX in children and toward using non-

Table 2 Osteosarcoma outcomes in various studies. (Source: Adapted from Ref. [3]; Other additional references: [46–48])

Author	*N*	Drugs	RFS/EFS% 5 year
Picci et al. (2010)	1656	Mtx–cisplatin–doxorubicin–ifosfamide	57
Ferrari et al. (2005)	182	Mtx–cisplatin–doxorubicin–ifosfamide	64
Daw et al. (2011)	75	Carboplatin–doxorubicin–ifosfamide	67
Fuch et al. (1998)	128	Mtx–cisplatin–doxorubicin	66
Okanegm et al. (2015)	108	Mtx–cisplatin–doxorubicin–ifosfamide	57
Ayan et al. (2009)	94	Cisplatin–doxorubicin–ifosfamide	65
Patel et al. (2002)	20	Cisplatin–doxorubicin–ifosfamide	68
Puri et al. (2017)	738	Cisplatin–Doxorubicin–ifosfamide	53
Bajpai et al. (2017)	209	Cisplatin–Doxorubicin–ifosfamide	60

Mtx Methotrexate, *RFS* Relapse-free survival, *EFS* Event-free survival

Table 3 Histological grading of osteosarcoma (adapted from the Ref. [49])

Salzer–Kuntschik grading	
Necrosis grade	Residual tumor cells
I	No viable appearing tumor cells
II	Single vital tumor cells or one vital cell cluster <0.5 cm
III	Vital tumor <10%
IV	Vital tumor 10%–50%
V	Vital tumor >50%
VI	No effect of chemotherapy
Huvos grading	
Necrosis grade	Residual tumor cells
IV	No viable-appearing tumor cells
III	Foci of viable tumor <10%
II	Tumor necrosis >50%
I	Little or no effect of chemotherapy

HDMTX among adults. HDMTX mandates complex pharmacokinetic monitoring, stringent hydration control and leucovorin administration in an inpatient setting [3]. It is more expensive and challenging to administer in resource constrained settings [21].

Chemotherapy-induced histological necrosis(HN) is considered the most robust prognostic marker and most widely accepted definition suggest that achievement of ≥90% necrosis signifies as good response. There are various standard grading systems to map the chemotherapy-induced HN; however, Huvos grading is widely accepted (Table 3) [22, 23].

Good responders, i.e., those who achieve a grade III or IV HN (Huvos grading), had superior outcomes. There were attempts to convert fate of poor responders by addition of chemotherapeutics in adjuvant phase, however, without success including in the large collaborative European and American Osteosarcoma Study Group (EURAMOS)-1 trial, wherein addition of ifosfamide and etoposide to existing three drug regimen did not improve outcome. Rather additional acute and chronic toxicities including second malignancies were observed [24].

Multiagent chemotherapy has substantially improved survival in osteosarcoma; however, since the last three decades, it has plateaued. Mifamurtide, an immunomodulator drug when added to chemotherapy has shown improvement in overall survival (albeit not event-free survival); however, it is not accepted as a standard due to lack of clarity about the trial design and results [25]. In EURAMOS-1 trial another immunomodulator drug interferon alpha-2b was tested in randomized fashion among good responders. Notably, the outcomes with MAP plus interferon alpha-2b were not superior to that of MAP alone arm, and hence, the strategy is not supported in standard osteosarcoma care [26].

Hence, a three-drug therapy essentially consisting of a cisplatin and adriamycin backbone along with either HDMTX or ifosfamide is recommended. Current evidence does not support changing chemotherapy on the basis of histologic response in localized osteosarcoma outside a clinical trial.

In low-grade (i.e., parosteal/juxtacortical and central) or intermediate-grade (i.e., periosteal) osteosarcoma, wide resection is the current standard. No adjuvant therapy is recommended. The indication for chemotherapy in periosteal (intermediate-grade) osteosarcoma is debatable.

6.2 Our Institute Practice for Osteosarcoma

At Tata Memorial Centre, the histologically diagnosed osteosarcoma patients undergo standard staging workup and testing to assess optimal organ function to administer chemotherapy (Fig. 5). The workup comprises of complete blood count, renal function (by serum creatinine and radionuclide 99m technetium diethylenetriaminepentaacetic acid [DTPA] scan), liver function test, echocardiography and pure tone audiometry. Additionally, nutritional parameters are monitored at baseline, post NACT and ACT and periodically in-between based on treating clinician's decision and nutritionist's referral is carried out and appropriate corrective measures are practiced inclusive of intravenous and oral supplements.

The Standard "OGS-12" chemotherapy protocol comprises of four cycles of NACT and four cycles of ACT in sequential cycles, delivered every 21 days (Table 4). The cumulative doses of the drugs used are: cisplatin 600 mg/m^2, Adriamycin 300 mg/m^2, and ifosfamide 54,000 mg/m^2, over eight doublet cycles with universal primary growth factor prophylaxis and nutritional support as appropriate to enhance compliance [3]. Appropriate-dose modifications are carried out as clinically indicated for relevant higher grade hematological and/or nonhematological toxicities. Patients are assessed for optimal surgical procedure with adequate oncological margins after NACT is completed. Chemotherapy-induced histological necrosis on the surgical specimen is assessed using Huvos necrosis grading; however, here is no change of therapy based on this response metric [23].

6.3 Prognostic Markers in Osteosarcoma

Extremity location, good histological necrosis, low-grade tumors, no metastasis, low serum alkaline phosphatase, and LDH are good prognostic markers, while older patients (>40 years), secondary osteosarcoma, multifocal tumor and loss of heterozygosity of RB gene are identified as poor prognostic markers [27–30]. VEGF expression, Her 2 expressions, noninvasive imaging variables and compliance to therapy have also been suggested as potential prognostic indicators.

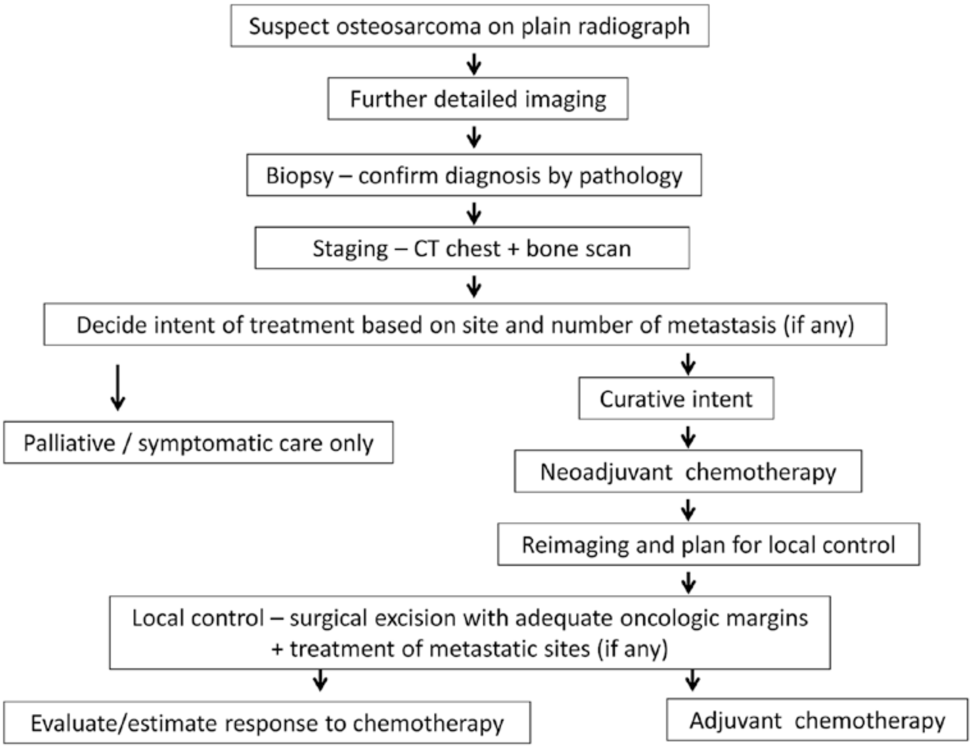
Suspect osteosarcoma on plain radiograph
Further detailed imaging
Biopsy – confirm diagnosis by pathology
Staging – CT chest + bone scan
Decide intent of treatment based on site and number of metastasis (if any)
Palliative / symptomatic care only
Curative intent
Neoadjuvant chemotherapy
Reimaging and plan for local control
Local control – surgical excision with adequate oncologic margins + treatment of metastatic sites (if any)
Evaluate/estimate response to chemotherapy
Adjuvant chemotherapy

Fig. 5 Flow chart of the work-up of a histologically diagnosed osteosarcoma as practiced at our center

Table 4 "OGS-12"—Osteosarcoma chemotherapy protocol (adapted from Ref. [3])

Schedule	NACT1	NACT2	NACT3	NACT4	Surgery	ACT5	ACT6	ACT7	ACT8
Cisplatin 100 mg/m^2 (Divided over 3 days)	√		XXX	XXX					
Adriamycin 75 mg/m^2 (Divided over 3 days)						XXX	XXX	XXX	XXX
Ifosfamide 9 g/m^2 (Divided over 5 days)	XXX	XXX							

NACT Neoadjuvant chemotherapy, *ACT* Adjuvant chemotherapy

6.4 Metastatic Disease

Nearly ~20% of osteosarcoma patients are having macrometastasis at the time of presentation. Majority of these are pulmonary (60%–70% lung alone) while skip or distant bone metastases are variably reported (up to 20%–30%) [31].

The *de-novo* metastatic patient who presents with isolated pulmonary metastases merits aggressive multimodality care inclusive of surgery, chemotherapy and pulmonary metastasectomy [32]. Evidence suggests that young patients with good ECOG performance status and unilateral pulmonary metastases may have comparable survival to those with localized disease [33].

6.5 Recurrent Disease

Patients who relapse with lung metastases after completing first-line treatment are evaluated for metastasectomy depending upon disease-free survival and resectability. Disease-free survival is an important independent predictor for outcome and distant failure within 2 years is a poor prognosticator. However, those who achieve a second complete remission still have a relatively good chance with ~40% five-year overall survival [34].

The role of second-line chemotherapy in relapsed disease is not well defined, and the choice of therapy depends upon prior utilized drugs, disease-free interval and often includes ifosfamide ± etoposide ± carboplatin, HDMTX and a few other potent drugs (e.g., gemcitabine and docetaxel; sorafinib). In two large series with unresectable metastatic recurrence, chemotherapy has demonstrated limited increment in survival statistics. However, there was a meaningful benefit noted in resectable disease among one of the two studies. In symptomatic disease, chemotherapy on several occasions offers good palliation with clinically meaningful benefit. Newer agents with higher activity are an active area of research in recurrent osteosarcoma [35]. Certain antifolate agents like trimetrexate, have been investigated in relapsed scenarios. Patients who received conventional doses of ifosfamide (9 g/m sq), may be re challenged with escalated doses (14 g/m sq) and on a subsequent relapse again, to 17.5 gm/m sq^2 with meaningful responses (Jaffe N, unpublished data). However, due to potential nephrotoxicity, the 17.5 g/m sq. should be limited to three courses (one course every 4 weeks) in divided doses and with adequate hematological support for myelosuppression [36].

6.6 Role of Radiation in Osteosarcoma

Osteosarcoma is generally not considered a radiation-sensitive tumor. In situations where tumors are not amenable for surgical excision, radiation with or without concurrent chemotherapy may be considered. For patients with inoperable primary disease, high-dose external beam radiation therapy (70 Gy/35#/7 weeks @ 2 Gy/fraction) with conformal techniques like 3-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) has resulted in satisfactory disease control without significant toxicity. Though still considered experimental, there is encouraging data on the role of proton and carbon ion therapy [37].

6.7 Future Directions

Osteosarcoma is a heterogeneous tumor, and hence, sequencing data did not show real benefit, and targeted therapies which focus on isolated aberrant signaling pathways are not successful. Tyrosine kinase inhibitors (TKI) have shown good activity in this challenging tumor, and potential kinase targets in osteosarcoma are VEGFR, PDGFR, mTOR and PI3K. An Italian phase 2 trial with oral TKI (sorafenib) along with everolimus has shown a clinically meaningful 45% 6-month progression-free survival, although the trial was statistically negative [38]. There is an unmet need and perhaps combined TKI therapy trial may enlighten us further. Osteosarcoma tumor cell ubiquitously expresses a cell surface marker GD2 and is a potential target. A large, multiplatform sequencing trial TARGET OS, from the National Cancer Institute, will provide right directions for future therapy. Despite that, there is some evidence that PD-L1 expression and tumor infiltrating lymphocytes are increased in osteosarcoma metastases and presence of tumor-associated macrophages are protective and associated with decreased metastasis, check point inhibitors are in an early phase of development and are considered experimental in this disease [39].

7 Chondrosarcoma

There is little role for systemic therapy in conventional chondrosarcomas. Dedifferentiated chondrosarcoma is associated with poor prognosis due to propensity to metastasize to bones and/or lung at presentation or early (within 12–18 months) [40]. Similar to osteosarcoma, adjuvant chemotherapy may be considered especially in the younger patients with no metastasis. At times, palliative use of cisplatin and doxorubicin may also provide meaningful clinical benefit especially in relatively good ECOG performance status in young patients. Another rare subtype is mesenchymal chondrosarcoma wherein surgical resection is primary treatment and adjuvant chemotherapy is similar to Ewing's sarcoma-type chemotherapy regimen. The drugs commonly used are vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide. Dedifferentiated chondrosarcoma is another rare subtype and although it is not very chemo sensitive tumor, is often treated as a high-grade bone sarcoma often with a combination regimen with doxorubicin and cisplatin or ifosfamide and trabectedin [31].

Similar to osteosarcoma, chondrosarcoma too is considered a radiation-resistant tumor. In situations where in tumors are not amenable for surgical excision, radiation may be considered [41].

8 Surgery in Bone Sarcomas

8.1 Principles of Extremity Reconstruction

The goal of curative treatment in bone sarcoma is to achieve local control and decrease the risk of systemic relapse. While neo/adjuvant chemotherapy along with surgical resection is the mainstay in osteosarcoma, surgery alone is the norm for chondrosarcoma. Curative intent of treatment is when R0 resection (no residual microscopic disease) is possible in a safe manner. Long-term results have shown limb salvage to have similar survival as an amputation [42]. The local control rates have also been consistently high. Limb salvage is thus the standard of care when a tumor can be excised with an adequate oncologic margin while preserving satisfactory function. Three centimeters of marrow margin as measured on a T1 weighted image and a layer of normal tissue all around the tumor is generally adequate. An adequate soft tissue margin is difficult to quantify in millimeters in a consistent manner. Certain natural tissue barriers like intermuscular septum, deep fascia, periosteum, growth plate, cartilage, vascular adventitia and epineurium are more resistant to tumor invasion and act as sufficiently negative margins close to critical structures [43]. Adequate function postresection, acceptable cosmesis, minimal pain, ability to continue activities of daily living and superior function to an amputation prosthesis are the goals of a successful limb salvage surgery. Often limb salvage is combined with metastasectomy for curative intent. The common barriers to limb salvage are poorly placed biopsy incisions (transverse, crossing multiple compartments), involvement of a major vessel or major motor nerve that precludes reconstruction, a displaced pathological fracture with contamination of multiple compartments, intractable infection and inadequate remnant motor function after resection [6]. Some of these factors are relative contra-indications in the modern multidisciplinary era. A pathological fracture is not an absolute contraindication for limb salvage. It often heals after neoadjuvant chemotherapy and permits adequate oncologic resection allowing limb salvage [44].

Reconstruction after resection of bone tumors involves replacing the bone and soft tissue defects to allow good function and promote reliable tissue healing. Since most bone sarcomas affect the metaphyseal or epimetaphyseal region of the long bone, osteoarticular resection is needed. Intercalary resections are performed for predominantly diaphyseal or meta-diaphyseal tumors when joints on either side can be saved. For certain low-grade sarcomas, hemicortical resections (removal of part of bone circumference) achieve good local disease control [45]. Reconstruction is thus determined by the nature of the defect. Intercalary defects can be reconstructed by autografts or allografts, reimplantation of sterilized tumor bone (methods of sterilization have included autoclaving, microwave, pasteurizing, liquid nitrogen and extracorporeal radiotherapy) or intercalary prosthesis (Fig. 6). Osteoarticular defects are most commonly reconstructed with endoprosthesis. Modern endoprosthetic systems are large metallic segments that replace the excised

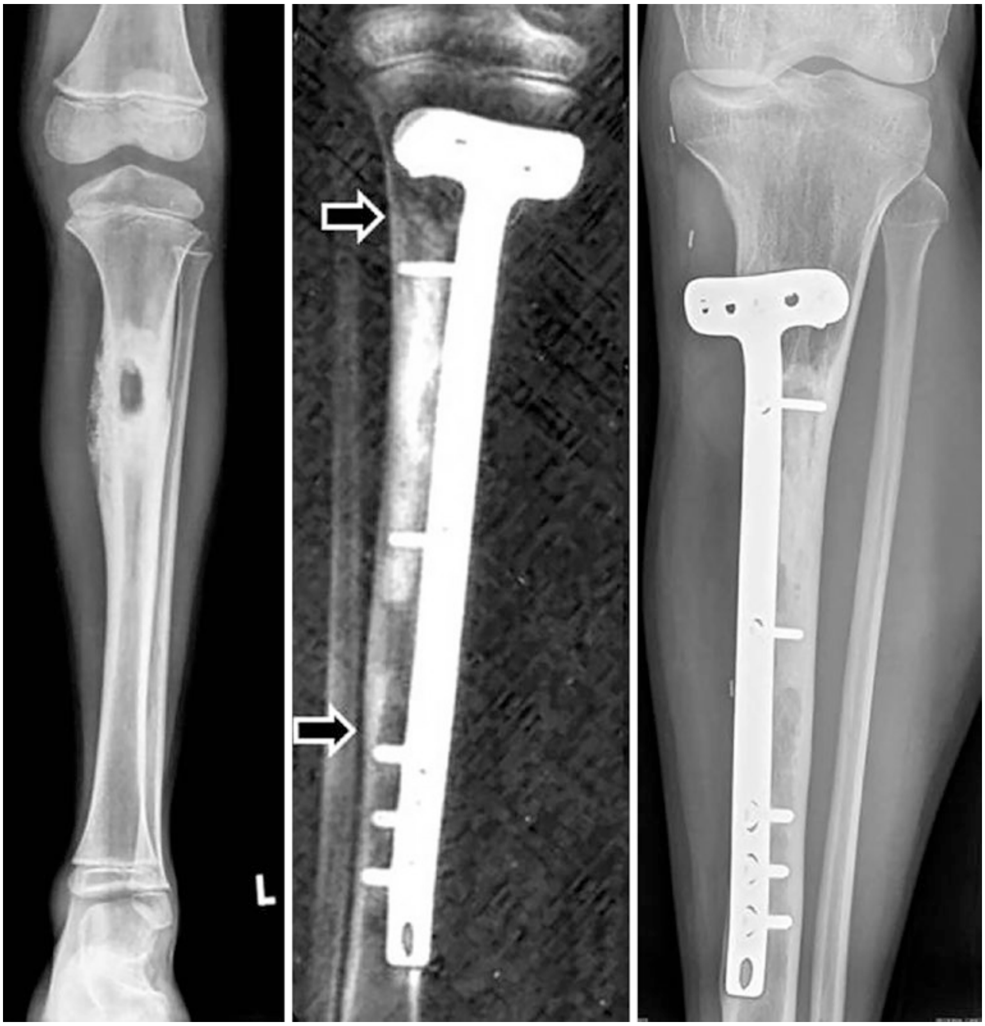

Fig. 6 Extracorporeal radiotherapy and reimplantation. Osteosarcoma of tibial diaphysis (left); resection and reimplantation (center arrows show osteotomy sites). Follow-up at 10 years with physeal growth having continued to occur (right)

bony segment and the adjacent joint (Fig. 7). They are modular and available off the shelf, thus allowing on-table reconstruction of defects of varying sizes. The rapid return to function and weight bearing, limited interference with adjuvant treatment in the form of chemotherapy or radiotherapy have made endoprosthetic systems the mainstay of extremity reconstruction. Allograft-prosthetic composites, osteoarticular allografts, joint fusion using bone grafts (arthrodesis) and rotationplasty are other methods of reconstruction after osteoarticular resection.

In children and adolescents an active growth plate that contributes to limb length is often involved or resected as tumor margin. This leads to significant limb length discrepancy at skeletal maturity. Rotationplasty though cosmetically not very appealing is an option that avoids the complication of limb length discrepancy. The most common site where rotationplasty is used is for tumors of the distal femur and proximal tibia. Patients undergo an en bloc excision of the distal femur and proximal tibia including skin and all surrounding soft tissues while maintaining the continuity of the neurovascular bundle. The bony limb continuity is then reestablished by fusing the tibia with the proximal femoral remnant after 1800 external limb rotation, thus allowing the ankle to function as the knee (Fig. 8). An expandable prosthesis can help overcome these problems. These are expensive, thus afforded by few in the LMIC (low–middle-income countries) and may need repeated revisions over the child's lifetime, thus increasing the risk of infection and other complications.

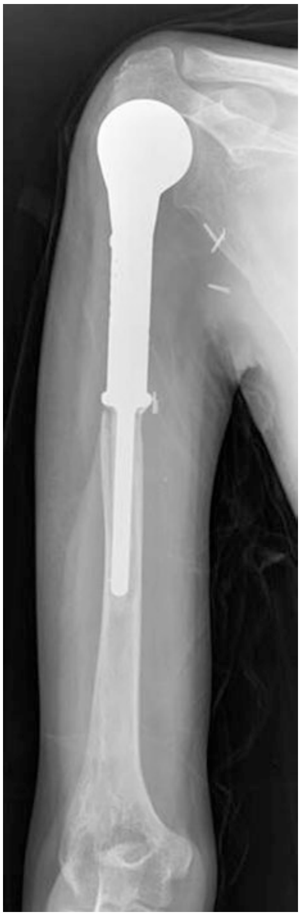

Fig. 7 Endoprosthesis. A proximal humerus prosthesis used to reconstruct the defect after tumor resection

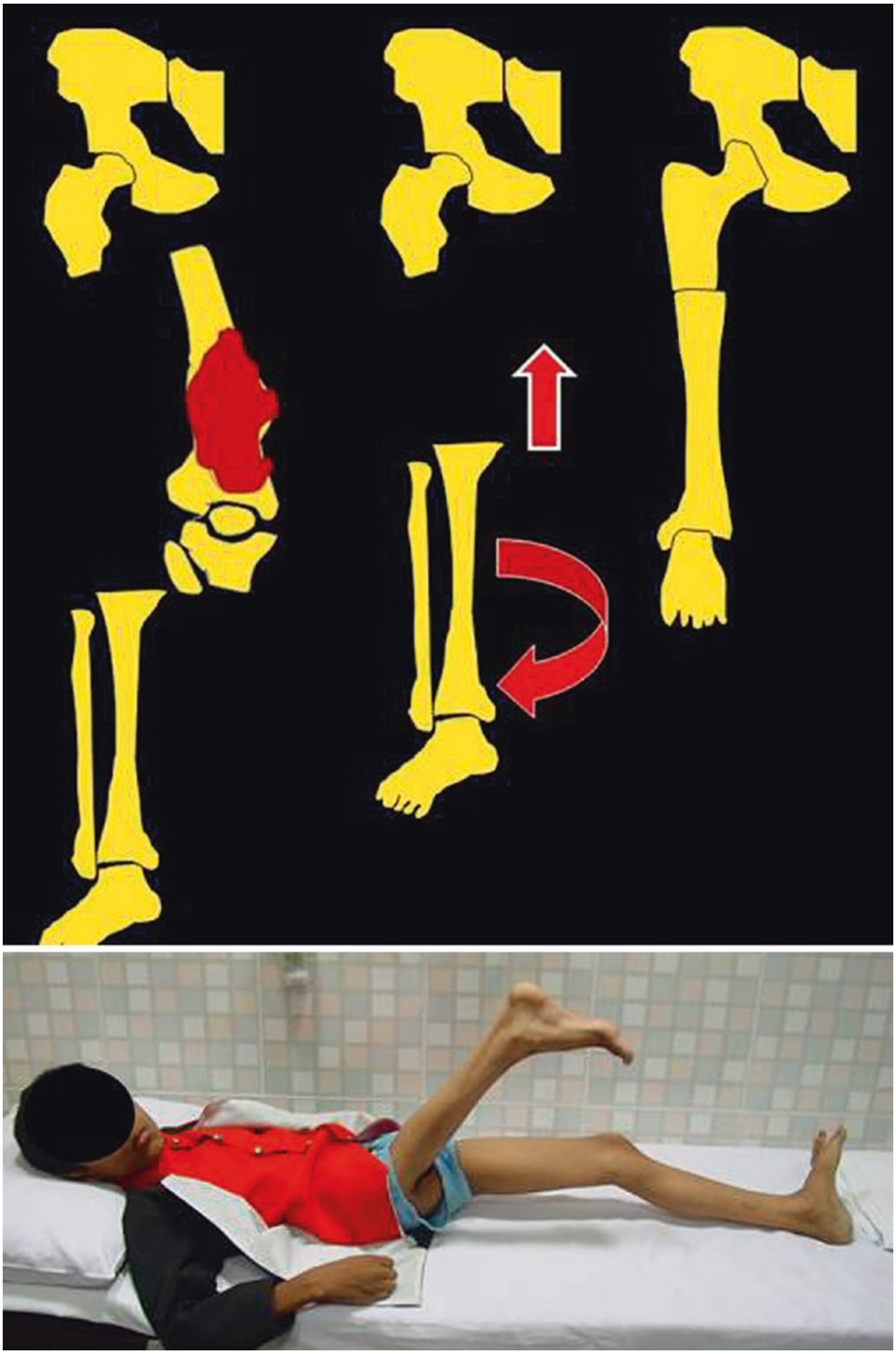

Fig. 8 Rotationplasty. Diagrammatic representation of a rotationplasty for a distal femur lesion demonstrating how the ankle functions as the knee

9 Surveillance and Follow-up

The aim of post treatment surveillance is to detect a recurrence or other treatment related toxicity (cardiotoxicity, ototoxicity, renal, fertility, function, second malignancy) early with the hope that early intervention will improve outcomes. It is unclear if aggressive surveillance modalities improve outcomes. Increased frequency of clinic visits and investigations is a huge resource, time and logistic burden. Another concern is cumulative radiation exposure. Most guidelines (NCCN, ESMO) recommend a 3–4 monthly follow up in the first 2 years, 6 monthly until 5 years and annually subsequently until year 10. Each visit involves a thorough clinical exam and history, radiograph of the operated area and a chest X-ray, and organ toxicity directed investigations. The only published on-inferiority randomized trial (TOSS) did not demonstrate a difference in outcomes with a lesser frequency of follow up (3 vs. 6 months) or modality of chest metastasis surveillance (CXR vs. CT) [46]. This study and other reports note that the majority of local recurrences are detected by the patient, and thus, pick up of asymptomatic radiologic local recurrence is unlikely. Once a recurrence is confirmed with a biopsy, cancer appropriate staging modality is used.

Apart from disease recurrence, it is essential to identify and manage other system toxicities as they have a significant impact on quality of life. It is best to have a dedicated clinic for long-term survivors whose concerns are different and not limited to disease status. Psychosocial support is an important part of surveillance, especially in the children, adolescent and young adult population.

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Soft-Tissue Sarcoma

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Abbreviations

BT	Brachytherapy
CT	Computed tomography
EBRT	External beam radiotherapy
IMRT	Intensity-modulated conformal radiotherapy
MRI	Magnetic resonance imaging
NCIN	National Cancer Intelligence Network
PET	Positron emission tomography
STS	Soft-tissue sarcoma
TNFα	Tumor necrosis alpha
USG	Ultrasonography

1 Introduction

Soft-tissue sarcomas (STS) are rare heterogeneous tumors of mesenchymal origin arising in connective tissues, representing less than 1% of adult malignancies [1]. Due to their varied subtypes, they are a challenge to diagnose and treat. Sarcomas are classified according to the "World Health Organization Classification of Tumours of Soft Tissue and bone" providing universal nomenclature for use worldwide. Each subtype of STS has common clinical, therapeutic and prognostic features. Extremities are the most common site for STS accounting to up to 60% followed by trunk (19%), retroperitoneum (15%) and head and neck (9%) [2]. Approximately 80% arise in soft tissue and rest from connective tissues within the bone. The etiology of most STS is still unknown. In few cases, genetic and environmental factors such as exposure to chemicals (e.g., vinyl chloride, arsenic), exposure to radiation, viral infection (Herpes virus), immunodeficiency (Epstein–Barr virus), prior injury (scars, burns), chronic tissue injury, neurofibromatosis and certain germ line mutations (Li–Fraumeni syndrome [p53 mutations], RB1 gene mutations) [2, 5] can lead to few variants of STS. Given their low incidence, most clinicians and pathologists have limited experience in their presentation, which can lead to delay in diagnosis and treatment [3, 4]. The overall 5-year survival rate for STS in extremities is 65–75% [5]. In this chapter, we outline the current principles of diagnosis and treatment protocols for STS.

2 Incidence and Epidemiology in India and Globally

The National Cancer Intelligence Network (NCIN) reports that the incidence of STS is approximately 45/million population per year (NCIN) [6]. In a study conducted at Tata Memorial Hospital over a period of 1 year, out of all the malignant lesions presented to bone and soft-tissue department (1382), 30% (587) were STS [7]. As most of the soft-tissue lesions are intervened by community surgeons, it is difficult to get an exact incidence.

3 Clinical Presentation in India and Globally

Majority of STS occur in adults (94% >20 years age), and apart from alveolar soft part sarcoma and leiomyosarcoma, all other subtypes have male predominance (1.5:1) [8]. Extremities account up to 60% of STS with lower limb being a more common location than upper limb with a distribution

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of 28% and 12%, respectively. Thigh is the most common site in the body accounting for 44% of all extremity STS [9].

Most common presenting complaint of STS is a painless, progressively increasing mass. At times, the patient may present with constitutional symptoms such as fever and/or weight loss. Some present with pain or symptoms associated with compression by the mass such as paresthesias or edema in an extremity. In case of pelvic and retroperitoneal sarcomas, they can present with a noticeable lump in the abdomen, increasing abdominal girth, pain, bleeding (hematemesis, melena, anemia) and obstruction. Superficial STS may present with fungation and bleeding.

Diagnosis of sarcomas of extremities is early compared to those in deep seated locations such as pelvic [10]. In developed countries, the presentation may be early compared to countries such as India where most of them presenting in advanced stages due to late presentation owing to ignorance and belief in other modalities of treatment other than modern medicine.

STS metastasize commonly to lung, and the patients can present with cough, shortness of breath, hemoptysis, pain or discomfort in chest and pleural effusion. Metastasis to bone is rare, and the most common complaint is pain [11].

4 Evaluation and Work-up

Evaluation of an STS involves detailed clinical examination, imaging to stage disease local and systemically and histopathological confirmation of subtype. Clinical evaluation includes estimation of the size of the lesion, location (superficial/deep), mobility and consistency. Palpation of the mass will help in determining the relationship to other anatomical landmarks. Local tenderness may be a sign of an inflammatory lesion. Pseudoaneurysm/vascular lesion can be ruled out by palpation/auscultation. A positive Tinel sign would indicate a nerve sheath tumor. Proximal draining lymph nodes should be examined for any lymphadenopathy. A soft-tissue mass exhibiting any of the following four clinical features should be considered to be malignant until proved otherwise: (1) Rapid increase in size, (2) size >5 cm, (3) location deep to the deep fascia, or (4) pain. The risk of malignancy increases with each factor with increasing size being best individual factor [12]. Benign or local grade lesion rarely metastasizes; hence, systemic evaluation may not be required.

4.1 Ultrasonography (USG)

Can be used for the evaluation of superficial STS and evaluate the size, depth and proximity to vital structures. It can also be used for screening of local draining lymph nodes to look for lymph node metastasis common in rhabdomyosarcoma, alveolar soft part sarcoma, clear cell sarcoma, epithelioid sarcoma, synovial sarcoma and angiosarcoma [13]. USG can act as a guide for tissue sampling in superficial masses.

4.2 Plain Radiograph

Plain radiograph has limited utility in evaluation of STS. The presence of calcification in a soft-tissue mass seen on a radiograph can point out toward a bone-forming sarcomas or synovial sarcoma [14].

4.3 Magnetic Resonance Imaging (MRI)

MRI is the preferred modality for evaluation of STS of extremities, trunk, head and neck as they provide multiplanar images with better spatial orientation. Signs such as deep-seated large mass, heterogeneous signal, surrounding edema and associated destruction of bone. In addition to stage the disease locally, MRI helps in planning biopsy approach and avoiding contamination of virgin compartments. They also help in surgical planning by determining the resectability of the tumor, extent of involvement and the proximity of neurovascular structures [15].

Lipomatous lesion is isointense to subcutaneous fat with no residual high signal intensity on T2-weighted fat-suppressed images and no internal complexity. A malignant transformation can be suspected when the lesion is greater than 10 cm, fat content being less than 75% and internal nodular enhancing components [16]. Tail sign on MRI can help distinguish myxofibrosarcoma from other myxoid-containing tumors [17]. Synovial sarcoma can be infiltrating or well defined. It has low signal intensity on T1-weighted images and heterogeneous signal intensity on T2-weighted images due to areas of necrosis, hemorrhage and calcifications. Reactive periostitis of the adjacent bone can be seen in 11–20% of our cases [18].

4.4 Computed Tomography (CT)

Though its role in local evaluation in extremities is less, non-contrast CT of the chest is essential to look for pulmonary metastasis which occur in approximately 10% of patients at presentation [10]. CT is the imaging of choice in retroperitoneal sarcomas or in cases where the lesion shows calcifications or cortical destruction. For deep seated lesions and heterogeneous lesions, CT or ultrasound guidance helps in targeting the most representative region [19].

4.5 Positron Emission Tomography-Computed Tomography

PET and PET CT are not routinely recommended for initial workup of STS [20]. PET/CT may be more useful in cases with recurrence of STS [21] and in suspected MPNST in a case with neurofibromatosis [22]. NCCN guidelines state that PET scan may be useful in prognostication, grading and determining response to neoadjuvant chemotherapy in STS [23]. As this study is based on a single institute study, the clinical utility of PET prior to surgical treatment is still unclear [24].

4.6 Recommendations for Local Evaluation

- Local MRI
- CT for retroperitoneal sarcomas

4.7 Recommendations for STAGING

- Non-contrast CT thorax
- USG of local draining lymph nodes
- MRI brain/spine in angiosarcoma and ASPS
- Whole body MRI + noncontrast CT thorax/CT thorax + abdomen + pelvis + MRI spine for myxoid liposarcoma

4.8 Biopsy

Histologic diagnosis of a soft-tissue mass is the gold standard for treatment planning. Biopsy should be done by the surgeon who will be doing final resection or should be done by someone aware of principles of treating sarcomas. Poorly placed biopsy scars can hinder with limb salvage procedures or may result in extensive surgery and increase morbidity. Core needle biopsy using a gun is the most preferred method [25]. CT or USG guidance can assist in deep seated lesions or to target a specific area in a heterogeneous lesion [19]. In cases where sample obtained by core needle biopsy is inadequate or not representative, incisional biopsy is considered for additional material. This material can be further used for tissue banking and research. Excision biopsy can be recommended for lesions <3 cm in size, superficial to deep fascia and away from critical structures [26] (Fig. 1). FNAC is not recommended in initial diagnostic evaluation of STS as it has a lower diagnostic accuracy, may not provide histologic subtypes or grade of sarcoma [27]. However, it has a role in confirming disease recurrence [28].

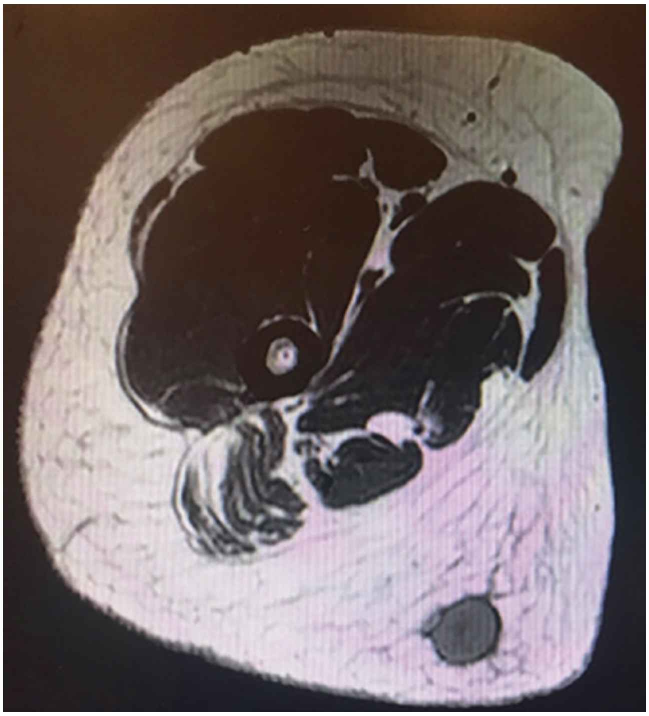

Fig. 1 Indication for excision biopsy

5 Pathology

WHO classifies them into more than 50 different histologic subtypes. The diagnosis of STS is based on the morphology. Immunohistochemistry (IHC) and monoclonal antibodies have been a major breakthrough in diagnostic evaluation for the pathologists. Fluorescent in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR) can be done to determine the molecular pathogenesis and confirm the histological diagnosis and also to identify subtypes within major histologic categories [29].

The tissue of origin is identified based on the immunohistochemical staining. The commonly used IHC is outlined in the Table 1.

They are either grouped according to the tissue of origin (e.g., liposarcoma, synovial sarcoma, angiosarcoma) or based on the architectural pattern (e.g., alveolar soft part sarcoma, epithelioid sarcoma). The common ones are outline in the Table 2. Most common subtypes are liposarcoma (15%), leiomyosarcoma (25%), synovial sarcoma (10%) and malignant peripheral nerve sheath tumors (6%) [2]. At Tata Memorial Hospital, synovial sarcoma was the most common histology (22.5%) with 24% being metastatic at presentation, followed by spindle cell sarcoma in 18.5% cases with 31% being metastatic at presentation. Soft-tissue Ewing sarcoma was in 12% of the cases with 50% of them having metastasis at presentation [7].

The commonly used histological grading system for bone and STS is the Fédération Nationale des Centres de LutteContre le Cancer grading system [30].

Table 1 Histology-specific IHCs

Desmin	Rhabdomyosarcoma, leiomyosarcoma
S100 antigen	Clear cell sarcoma, MPNST
Cytokeratin	Synovial sarcoma, epithelioid sarcoma
Factor VIII antigen	Tumors of endothelial origin

Table 2 Tumor types based on origin

Tumor Types	Subtypes	
	Benign	Malignant
Adipose	Lipoma	Well-differentiated liposarcoma Myxoid liposarcoma
Fibrous	Nodular fasciitis Deep fibromatosis	Fibrosarcoma Inflammatory fibrosarcoma Postradiation fibrosarcoma Cicatricial fibrosarcoma
Cartilage and bone forming	Extraskeletal chondrosarcoma	Extraskeletal osteosarcoma
Skeletal muscle	Rhabdomyoma	Alveolar rhabdomyosarcoma Embryonal rhabdomyosarcoma Ectomesenchymoma
Smooth muscle	Leiomyoma	Leiomyosarcoma Epithelioid leiomyosarcoma
Vascular	Hemangioma	Angiosarcoma Hemangioendothelioma Hemangiopericytoma
Nerve sheaths	Schwannoma Neurofibroma	Malignant schwannoma Neuroepithelioma Malignant granular cell tumor Malignant peripheral nerve sheath tumor
Synovial tumors		Synovial sarcoma Malignant giant cell tumor of tendon sheath
Pleomorphic tumors		Myxofibrosarcoma Angiomatoid fibrous histiocytoma

6 Staging

The staging system primarily used for STS is the American Joint Committee on Cancer (AJCC) or Enneking musculoskeletal tumor society staging system [31, 32]. AJCC grades them based on the size, nodal and distant metastasis nature, whereas Enneking uses the location of the tumor apart from grade and metastasis nature.

7 Referrals Including Genetic Counseling

Identification of an inherited gene alteration will not only help in early detection and cancer prevention, but also help in deciding the treatment protocols. Recognition of cancer genetic predisposition syndromes will allow patients and family members to under genetic testing and counselling to identify those at risk [33]. The patient usually have a family history of malignancies. Table 3 shows the common cancer predisposition syndromes associated with sarcomas [33].

Table 3 Familial inherited syndromes

Inherited syndrome	Inheritance	Genes	Chief clinical features	Associated sarcomas
FAP	AD	APC at 5q21-22	Thousands of colonic adenomatous polyps with colon cancer at age <40 years, osteomas, hepatoblastomas	Desmoid tumors
Li–Fraumeni syndrome	AD	TP53 at 17p13.1, CHEK2 at 22q12	Predisposition to early onset on multiple cancers, premenopausal breast cancer, STS, osteosarcoma, leukemias and adrenocortical carcinomas	Osteosarcoma, RMS, STS
Hereditary retinoblastoma	AD	RB1 at 13q14.2	Retinoblastoma, often bilateral and in early childhood (<5 years age)	Osteosarcoma, STS
Multiple osteochondromas	AD	EXT! at Bq24, EXT2 at 11p11	Multiple Osteochondromas	Chondrosarcomas
NF1	AD	NF1 at 17q11.2	Café-au-lait spots, neurofibromas, iris hamartomas (Lisch nodules), optic gliomas, skeletal abnormalities	MPNST, GIST, RMS

8 Principles of Management

Omnipresent in their site of origin, STS require multimodality treatment with patients managed at speciality centers (sarcoma referral centers) faring better than those treated elsewhere. Multidisciplinary team (MDT) consisting of pathologist, radiologist, surgeon, radiation therapists and medical oncologists form an integral part in treatment and decision making [34]. Table 4 shows the treatment plan for STS followed at Tata Memorial Hospital.

Histologically, four categories of margins have been described, namely: intralesional, marginal, wide and radical [35].

Intralesional: Margin runs through tumor leaving behind macroscopic disease. This can be done for palliative reasons or can be a result of unplanned excisions.

Marginal: Here, the surgical plane runs through pseudocapsule (reactive zone). As the reactive zone with tumor satellites is left behind, there are high chances of local recurrence rate.

Wide: The entire tumor is removed with a cuff of normal tissue measuring around 1–2 cm. If the soft tissue is adjacent to bone, it might warrant removal of a part of the bone to achieve wide margins.

Radical: This includes removal of the tumor along with the affected compartment. Though the chances of local recurrence are the least in radical resections, this is not routinely performed due to high morbidity. The most common indication for radical resection is local recurrence [36].

According to AJCC, the margins are classified as follows:

- R0—Margins free of disease
- R1—Microscopic tumor positive at inked border of the specimen
- R2—Gross tumor positive margin

There is another classification system, R + 1 mm classification [37], in which margins are classified as follows:

- R0—At least 1 mm of normal tissue between the tumor and inked margin
- R1—Tumor within 1 mm of the inked border
- R2—Grossly tumor positive margin

In a recently published study, the authors concluded that a negative but 1-mm margin may be adequate with multidisciplinary treatment. A planned close but ultimately positive margin along vital structures such as neurovascular bundles or bone increased risk for LR. Cases with inadvertent positive margins were associated with highest risk of local recurrence [37].

Table 4 How we do it at TMH

Grade	Depth	Treatment
Low	Superficial	Surgery
Low	Deep	Surgery (Ext RT only if margins close; <1 cm on gross intraop findings or if microscopic margins +)
High	Superficial/deep	Surgery + Brachy + Ext RT NACT—In metastatic cases/ borderline resectable chemosensitive tumors

9 Surgical Management

The standard principle is wide excision which refers to removal of tumor with rim of normal tissue. In high-grade tumors, to avoid local recurrence, resection should be done beyond the reactive zone. Usually a margin of 2 cm is considered adequate for STS. Here, Kawaguchi's concept of barrier effects is an effective reference for local planning [38]. Thick barriers such as iliotibial band, presacral fascia, periosteum of infant or a child and joint capsule are given weightage of 3 cm of normal tissue. Weaker membranous tissue of muscle fascia, the periosteum of an adult, vessel sheath and epineurium are considered thin fascia, which are considered equal to 2 cm of normal tissue. In cases where the tumor is adhered to the membranous barrier and the outer surface still retains its original luster, then 1 cm is deducted from its original value, which should be compensated for by including a cuff of normal tissue.

If surgery is the sole modality of treatment, the margin should be at least 1 cm in all directions or include a fascial barrier. In cases where the tumor is close to vital neurovascular structures, marginal excision combined with adjunct radiotherapy can be performed. In patients presenting with unplanned positive margin resections, re-excision should be planned if complete clearance can be achieved.

Macroscopic residual disease leads to poor outcomes even with additional postoperative radiotherapy [39]. Unresectable tumors and borderline resectable tumors (because of size or close to vital structures) can be subjected to neo-adjuvant chemotherapy or radiotherapy or both based on their histology [40]. When the mass is close to vital anatomical structures (major nerves or vessels), a planned positive resection can be done or upfront resection and reconstruction can be planned [37]. The aim of preoperative radiotherapy is to devitalize the margins of an anticipated marginal excision (Fig. 2).

Resections associated with compartectomy or significant soft-tissue loss will need reconstruction with free or pedicle muscle transfer. In STS cases wherein an unplanned excision was done (Whoop's excision), tumor bed excision should be considered with postoperative radiotherapy (high-grade cases) [41].

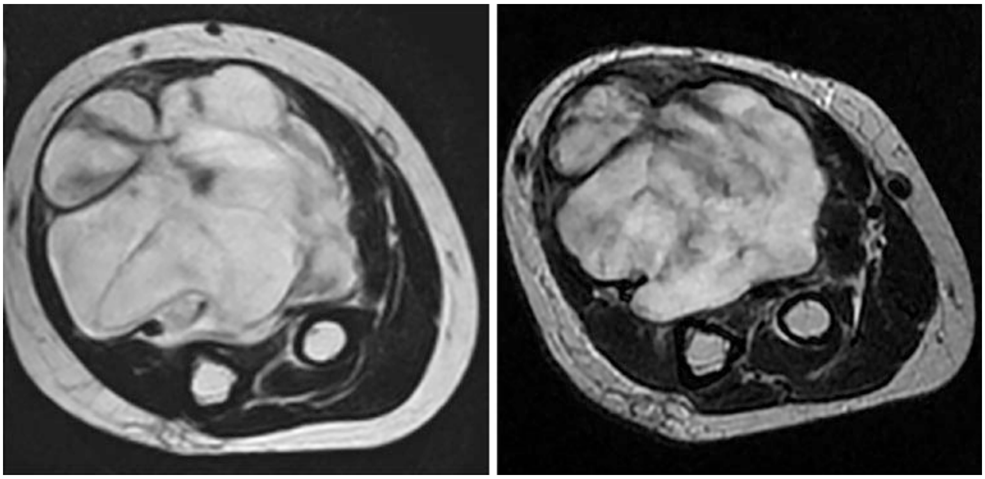

Fig. 2 A 25-year-old patient with a synovial sarcoma of the forearm close to the neurovascular structures. MRI images showing pre-RT and post-RT images

Despite multimodality treatment, sometimes localized tumors which cannot be resected completely may need an amputation to minimize the distant relapse. Amputation can also be offered in patient with multiple relapses, untreatable pain, bleeding or fungation [10].

10 Medical Management

Histology of the tumors helps deciding the role of chemotherapy in STS [42], but routine use in STS remains inconclusive [12]. High-grade tumors have the greatest tendency to metastasize, and such patients are most likely to benefit with chemotherapy [10]. The decision for preoperative chemotherapy should be a multidepartmental joint clinic decision. High-grade tumors which are borderline resectable and tumors wherein radiotherapy is not feasible qualify into this category. Neoadjuvant chemotherapy helps in assessing the histologic response to chemotherapy in an excised tumor allowing for detection of poor responders who may need an altered management [43].

To date, the largest trial of adjuvant chemotherapy for STS has failed to demonstrate any clear benefit from chemotherapy in local control, relapse-free survival or overall survival in patients treated with adjuvant chemotherapy [12]. The improved survival can be attributed to improved surgical techniques and increased use of adjuvant radiotherapy. As per NCCN guidelines [23], it is suggested that the need for adjuvant therapy be individualized on case to case basis. The other factors to be taken into consideration are patients performance status, comorbidities, disease location, tumor size and histologic subtype. Based on the meta-analysis from the Sarcoma Meta-Analysis Collaboration [44], a treatment regimen consisting both doxorubicin and ifosfamide significantly prolonged survival in patients post resection of extremity sarcomas. Adjuvant chemotherapy provided, small but definite risk reduction in local recurrence, distant recurrence and overall recurrence [44].

Table 5 Chemosensitivity of STS

Chemotherapy integral to management	Ewing's sarcoma family tumors Embryonal and alveolar rhabdomyosarcoma
Chemosensitive	Ewing's sarcoma family tumors Embryonal and alveolar rhabdomyosarcoma Desmoplastic small round cell tumor Synovial sarcoma Myxoid/round cell liposarcoma Uterine leiomyosarcoma
Moderately chemosensitive	Pleomorphic liposarcoma Epithelioid sarcoma Pleomorphic rhabdomyosarcoma Leiomyosarcoma Angiosarcoma
Relatively chemoinsensitive	Malignant peripheral nerve sheath tumor Myxofibrosarcoma Dedifferentiated liposarcoma Clear cell sarcoma Endometrial stromal sarcoma
Chemoinsensitive	Alveolar soft part sarcoma Extraskeletal myxoid chondrosarcoma

Table 5 shows the chemosensitivity of various STS [12].

10.1 Isolated Limb Perfusion

Isolated limb perfusion can be useful to downgrade the tumor and facilitate excision of STS in the extremities. The technique involves the use of local high-dose chemotherapy (melphalan), tumor necrosis alpha (TNFα) and hyperthermia. Using arterial and venous cannulation and a tourniquet, the affected limb is exposed to high quantities of these substances and has shown to shrink the tumor [45].

11 Role of Radiation in the Management of Soft-Tissue Sarcomas

Radiotherapy is an important adjunct to surgery for optimal local control and making limb salvage feasible. It can be in the form of preoperative radiotherapy or adjuvant radiotherapy. Adjuvant radiotherapy remains the most common form of radiation used for these tumors. The role of adjuvant radiotherapy was established more than three decades back, when three randomized controlled trials reported improvement in local control when offered as a part of limb salvage treatment [46]. The landmark NCI trial reported that the addition of adjuvant radiotherapy reduced local recurrences whereas the overall survival was similar to patients undergoing limb sparing surgery only [46]. Although the benefit was seen more in high-grade tumors, low-grade tumors also showed a significantly lower probability of local relapse [46]. A 20-year follow-up of the same study confirmed the above findings of excellent local control with acceptable treatment-related morbidity and no statistically significant improvement in overall survival [47]. Recent publications with large patient numbers have reported that adjuvant radiotherapy is associated with improved overall survival [48]. Low-grade, small (T1) tumors with negative margins can be treated with wide local excision alone; however, low-grade, T1 tumors with known adverse factors (like positive margins) and all high-grade, T2 tumors would benefit from the addition of radiation [46].

Adjuvant radiotherapy can be in the form of external beam radiotherapy (EBRT) or perioperative interstitial brachytherapy (BT). BT has been demonstrated to be an effective method of delivering adjuvant radiotherapy and has the benefit of shorter overall treatment time and smaller treatment volumes as compared to EBRT (Fig. 3) [49]. However, because it is a complex and labor-intensive technique, it is relatively less used. Though most of the Centre's practice conventional EBRT (Fig. 4), conformal radiotherapy in the form of intensity-modulated conformal radiotherapy (IMRT) has shown improved local control as well as favorable morbidity profile (Fig. 5) [50]. A nonrandomized comparative study from MSKCC reported local control significantly better with IMRT as compared to BT [51].

Preoperative radiotherapy has the potential of improving surgical margins and encouraging limb salvage in borderline resectable cases. The observed increase in the incidence of wound complications as compared to adjuvant radiotherapy and the imposed delay of surgical treatment, limits its use in our setting [52]. However, it is noteworthy that these acute wound complications though severe at times, are temporary. Contrary to this, the late complications of adjuvant radiotherapy like fibrosis, arthrosis and edema can be frequently progressive in nature [53]. A recently published national cancer database analysis report points toward higher rates of R0 resection for patients receiving preoperative radiotherapy and that negative surgical margins are associated with improved overall survival [54]. Utilization of improved radiotherapy

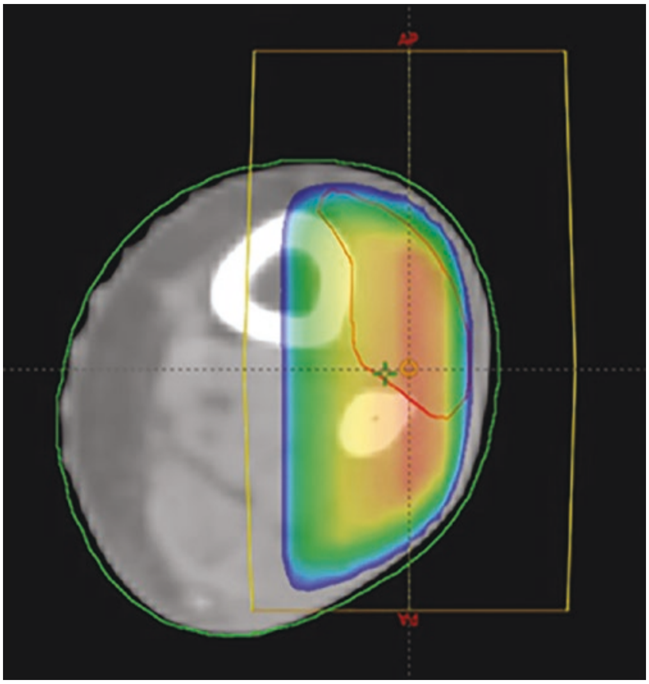

Fig. 4 Conventional radiotherapy dose distribution

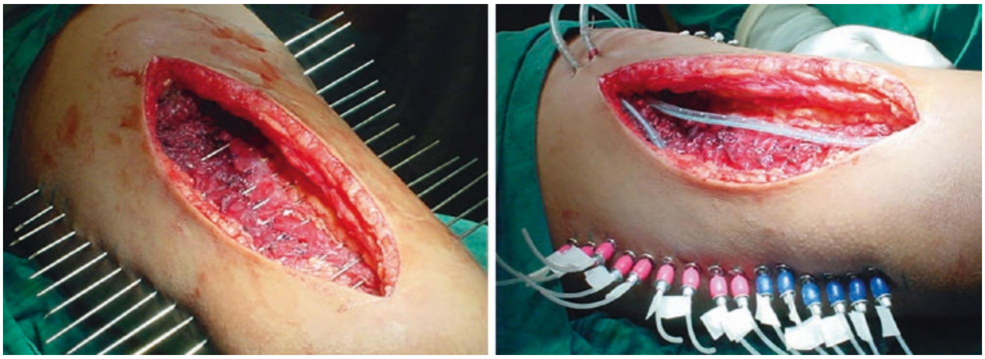

Fig. 3 Perioperative interstitial brachytherapy

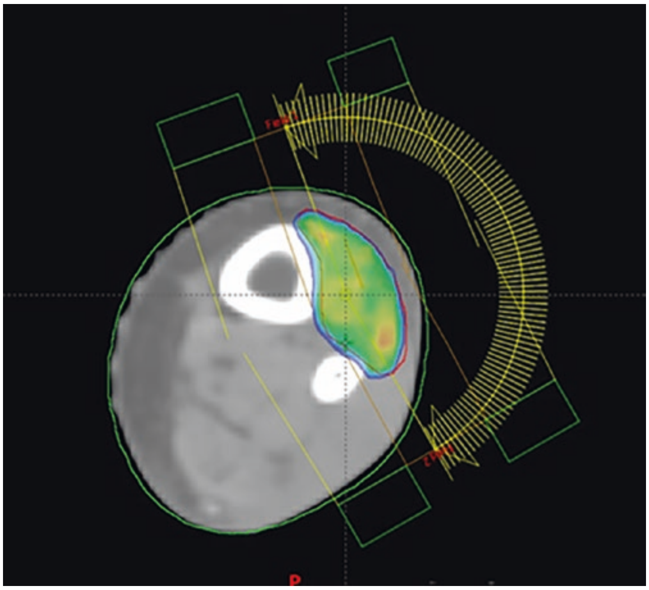

Fig. 5 Conformal radiotherapy dose distribution

technique (IMRT, image-guided and adaptive radiotherapy) is associated with significantly reduced incidence of wound complications [55]. The standard dose of radiation therapy ranges between 50 Gy/25#/5 weeks @ 2 Gy/fraction in the preoperative setting to 60–66 Gy/30–33#/6–7 weeks @ 2 Gy/ fraction in the postoperative setting.

As per NCCN guidelines, preoperative chemotherapy alone or preoperative radiotherapy alone or preoperative chemoradiation are all acceptable options. There are no data to support one over the other; if possible, these patients should be treated in context of a clinical trial.

12 Prognosis

Prognosis depends on grade, size, depth, age and histology of the tumor. There are well established nomograms that estimate the prognosis fairly well [56]. Local recurrence is related to grade, margins of excision and exposure to radiotherapy. In most cases, recurrences will arise within the first 5 years following treatment, and late relapses may occur in large tumors [57, 58].

13 Surveillance

There is no specific protocol for surveillance posttreatment due to lack of literature. The frequency and modality of imaging during flow-up remains controversial. Following a unique non inferiority trial conducted at our own institute we have concluded that a less intensive (chest X-ray) follow-up regime was not inferior to a more intensive regime (NCCT thorax) in patients treated for extremity sarcomas. In most cases, a chest X-ray at 6-month intervals and patient education regarding local examination of the surgical site will detect most recurrences without deleterious effects on eventual outcome [58]. Six-month follow-ups are advised for the first 5 years followed by yearly follow-up for the next 5 years.

14 Management of Recurrent Disease Including Specific Palliative Measures

Propensity for hematogenous dissemination is the most life-threatening aspect of sarcomas. Fifty percent of patients with high-grade sarcomas develop distant metastases and have a median survival of 12–19 months from diagnosis of metastases [59]. Though majority of patients who develop metastases are incurable, patient who can be treated with curative intent should be carefully selected. If the relapse is limited to local site, then the treatment would involve wide local excision with soft-tissue reconstruction procedures (depending on the extent of surgery). If the relapse is in the regional lymph nodes, nodal dissection is warranted with excision extending one level above the level of disease.

In cases with resectable pulmonary metastases, the reported 5-year survival is 25–40%. The recommended selection criteria for those undergoing pulmonary metastasectomy are as follows [60]:

- R0 resection should be feasible
- Primary disease should be controlled or controllable
- Absence of extrapulmonary metastases
- Physiological reserve in the patients to withstand the procedure

In patients with unresectable disease or with wide spread disseminated disease, chemotherapy is given with palliative intent with the goal of decreasing tumor bulk, symptomatic relief, better quality of life and prolonging survival. Apart from chemotherapy, surgery, radiotherapy and radiofrequency ablation can be considered in symptomatic metastases or in an attempt to prolong remission. Other drugs providing symptomatic relief included bisphosphonates or denosumab. It is advisable to involve specialists in palliative care to help benefit those who are critically ill.

How We Do It at TMC (Figs. 6 and 7)

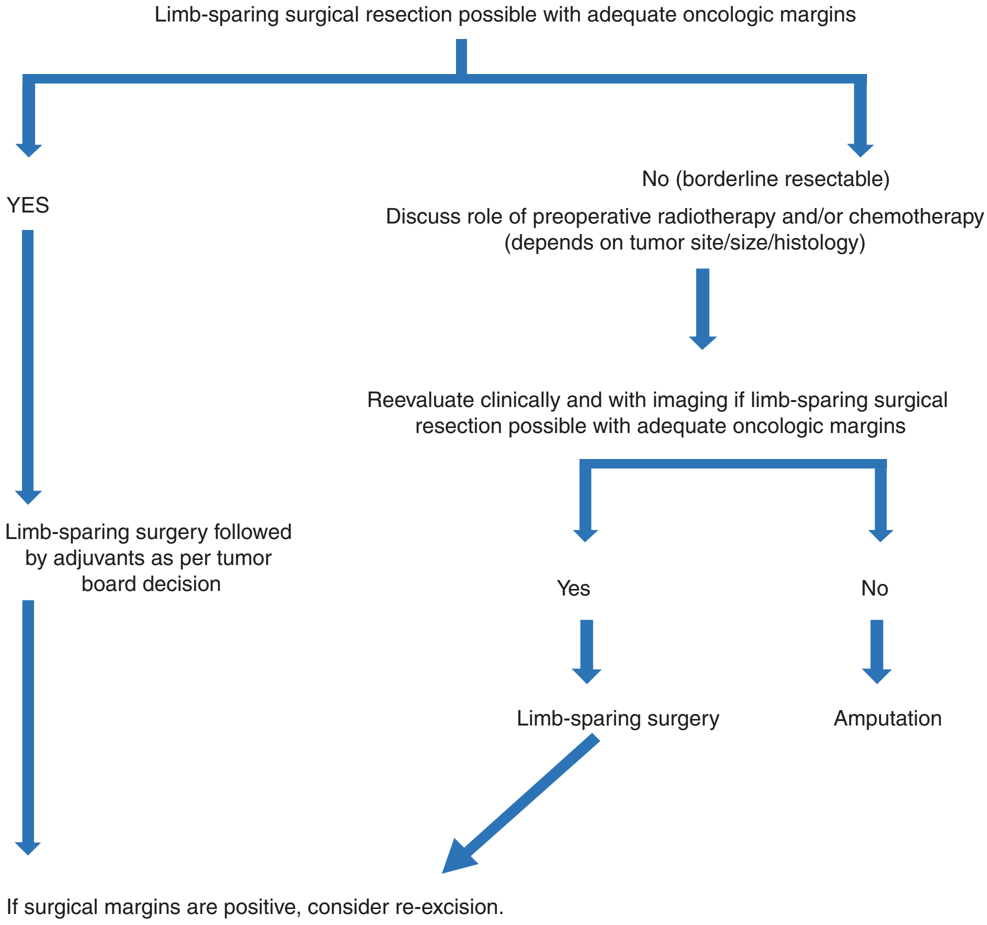

Fig. 6 Extremity soft-tissue sarcoma—nonmetastatic at presentation

Limb-sparing surgical resection possible with adequate oncologic margins
YES
No (borderline resectable)
Discuss role of preoperative radiotherapy and/or chemotherapy (depends on tumor site/size/histology)
Reevaluate clinically and with imaging if limb-sparing surgical resection possible with adequate oncologic margins
Limb-sparing surgery followed by adjuvants as per tumor board decision
Yes
No
Limb-sparing surgery
Amputation
If surgical margins are positive, consider re-excision.

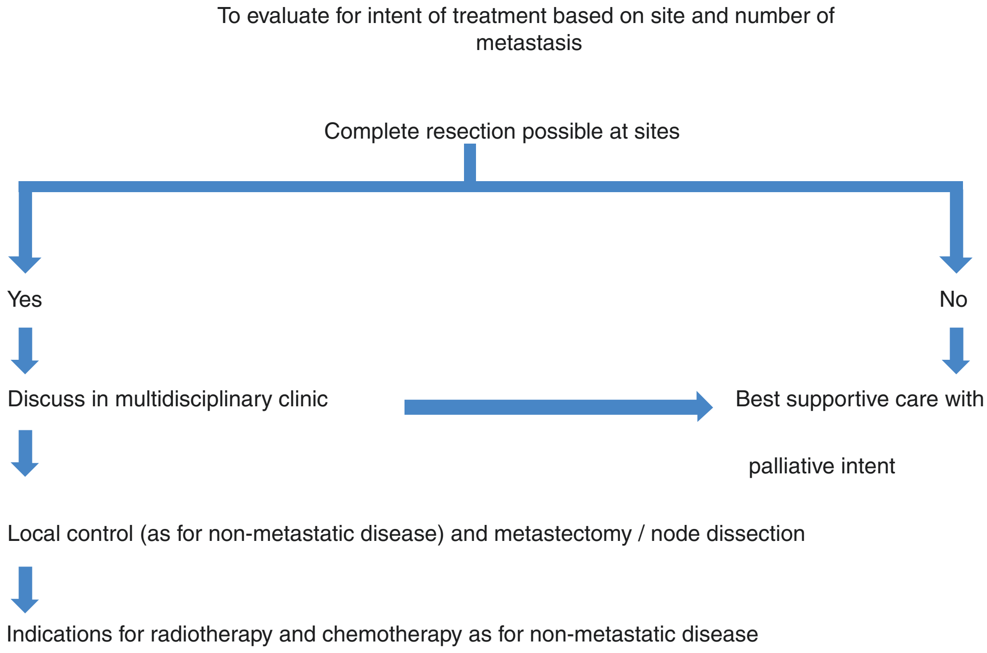

Fig. 7 Extremity soft-tissue sarcoma—metastatic at presentation

To evaluate for intent of treatment based on site and number of metastasis
Complete resection possible at sites
Yes
No
Discuss in multidisciplinary clinic
Best supportive care with palliative intent
Local control (as for non-metastatic disease) and metastectomy / node dissection
Indications for radiotherapy and chemotherapy as for non-metastatic disease

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Ewings Sarcoma

Tushar Vora and Siddhartha Laskar

Abbreviations

3D-CRT	3-Dimensional conformal radiation therapy
CCLG	Children's Cancer and Leukaemia Group
CT	Computerized tomography
ES	Ewing sarcoma
FDG-PET	Fluorodeoxyglucose positron emission tomography
GPOH	German Pediatric Oncology and Hematology Group
IMRT	Intensity-modulated radiation therapy
LDH	Lactate dehydrogenase
MRI	Magnetic resonance imaging
PNET	Primitive neuroectodermal tumor
POG	Pediatric Oncology Group
RT	Radiation therapy

1 History

James Ewing, an American pathologist, described "diffuse endothelioma of bone," characteristically different from the then well-known osteosarcoma, in 1921 (2 years after the publication of the first edition of his cancer textbook), in the radius bone of a 14-year-old girl [1]. After the failure of initial treatment with Coley's toxin, the tumor was treated with 12,760 millicurie hours of radium every 2 weeks for three doses leading to "surprising disappearance" of the tumor at the end of 5 weeks. Further, Ewing distinguished his series of six similar cases of bone tumors (tibia, ulna, ischium, skull and scapula [aged 14–19]) from osteosarcoma as "A large portion or the whole of the shaft is involved, but the ends are generally spared, contrary to the rule with osteogenic sarcoma. The shaft is slightly widened, but the main alteration is the gradual diffuse fading of the bone structure. Bone production is entirely absent. The radiograph is therefore rather specific." Another eponym associated with Ewing Sarcoma is the Codman's triangle, the periosteal elevation and calcification associated with bone tumor, first described by the British Pathologist, Ernest Codman. Even after almost a century of its initial description, most of the characteristics described by James Ewing and Ernest Codman, based only on a few case reports, have withstood the test of time. Interestingly, it was Ernest Codman who coined the term "Ewing sarcoma."

Historically, Ewing sarcoma (ES) was also among the first solid tumors to demonstrate chemo-sensitivity in the 1960s [2–4]. The characteristic chromosomal translocation of EWS-FLI1 was identified in the 1980s and similar translocations in histologically distinct primitive neuroectodermal tumors helped consolidate them into a common family in the next decade [5–7].

2 Epidemiology

Ewing sarcoma is the second most common bone malignancy, after osteosarcoma. This is predominantly a disease of adolescence, characterized by a median age of presentation of 15 years and most cases occur in the second and third decade of life, with a slight male preponderance. The reported frequency in population younger than 20 years is 2.9/million [8]. The unusual predilection in the Caucasians is another striking characteristic of Ewing sarcoma (six times more frequent than African Americans) and is partially explained by the shortening of Intron 6, near the breakpoint region of EWS in African population [9].

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Table 1 EWS gene rearrangement in Ewing sarcoma and other malignancies

Ewing sarcoma			
Partner of EWSR1	Chromosome	% of ES	Reference
FLI1 (Friend leukemia virus integration site 1)	11q24	85	[5]
ERG (ETS (Erythroblast transformation specific)-related gene)	21q22	10	[11]
ETV1 (E Twenty Six)	7p21	<1	[12]
E1AF (ETV4 or PEA3—Polyoma enhancer activator 3)	17q12	<1	[13]
FEV1 (Fifth Ewing variant)	2q33	1	[14]
Other malignancies			
Partner of EWSR1	**Chromosome**	**Malignancy**	**Reference**
PBX1 (pre-B cell leukemia homeobox 1)	1q23	Myoepithelial tumor	[15]
CREB1 (cAMP response element binding protein 1)	2q33	Clear cell sarcoma of soft parts	[16]
DUX4 (double homeobox protein 4)	4q35	Rhabdomyosarcoma	
WT1 (Wilms tumor 1)	11p13	Desmoplastic small round cell tumor	[17]
ZNF384 (Zinc finger protein 384)	12q13.31	Acute leukemia	[18]
DDIT3 (DNA-damage-inducible transcript 3)	12q13.3	Myxoid liposarcoma	[19]
NR4A3 (nuclear receptor subfamily 4 member 3) or MINOR (mitogen-induced nuclear orphan receptor)	9q31	Extraskeletal myxoid chondrosarcoma	[20]

3 Biology and Histology

Unlike Osteosarcoma, which is known to harbor astounding genetic heterogeneity, Ewing sarcoma is characterized by a relatively simple karyotype, most common being a reciprocal chromosomal translocation between chromosomes 11 and 22 (t(11;22)(q24;q12) in about 85% of cases [10]. The other possible translocations, involving the ews gene on chromosome 22 and leading to Ewing sarcoma, are described in Table 1, which together can be diagnostic for about 98% of Ewing sarcoma cases [11, 12]. Hence, the demonstration of EWSR1 break apart mutation, demonstrating *ews* gene rearrangement, by fluorescent in-situ hybridization technique, can be pathogenomic for majority of patients of Ewing sarcoma.

The classical EWS-FLI1 rearrangement results in the translocation of the 3′ portion of *fli1* (friend leukemia virus integration site 1) gene from chromosome 11 to the 5′ portion of the *ews* (Ewing sarcoma) gene on chromosome 22. The demonstration of this rearrangement correlates with the high expression of CD99 (MIC2), a cell surface sialoglycoprotein [21, 22]. A CD99 negative but t(11;22)(q24;q12) positive Ewing sarcoma has never been observed [23, 24].

Though the histogenesis of this tumor is still debatable, ES are among the small round blue cell tumors. The gross appearance of ES is that of a permeative, destructive growth in a bone with cortical infiltration, periosteal reaction and soft tissue extension. They have a fleshy, whitish appearance with variable tumor necrosis, cystic degeneration and hemorrhage [25]. Bone formation in response to chemotherapy may be visible but in much lesser proportion as compared to that in osteosarcoma. Extraosseous ES has similar morphology. They demonstrate a gradient of neuroglial differentiation; with poorly differentiated ES at one end and the more mature peripheral primitive neuroectodermal tumors (pPNET) at the other [1, 26, 27], though without any here-to-known therapeutic or prognostic significance. Strong diffuse membranous staining for cell-surface glycoprotein p30/32MIC2 (CD99) is characteristic of both and is present in 95–100% of the reported series, in addition to vimentin [28]. pPNET may show immunoreactivity for neuron-specific esterase (NSE), S-100 protein and Leu-7 [29]. Other Immunohistochemistry markers may be used to differentiate from neuroblastoma (positive for NSE, S-100 and Leu-7 but negative for Vimentin), lymphoma (positive for CD99 but also for leucocyte specific antigen CD45 (negative in ES), rhabdomyosarcoma (may be focally/weakly/cytoplasmic positive for CD99 but also positive for myogenin, myoD1 and desmin). Distinction from certain variants of synovial sarcoma (poorly differentiated small cell) may be difficult and molecular genetic testing for specific pathogenomic markers may be necessary [30].

4 Clinical Presentation and Staging

Ewing sarcoma cases have been reported in all age groups, but majority of the patients are adolescents at the time of presentation [31]. Pain, often loco-regional, is the predominant presenting complain, which characteristically does not resolve completely even during sleep [32]. Due to age associations, pain is often attributed to sports-related injuries or everyday activities or “growth spurts”. Pain, that is unexplained and not attributable to a defined trauma, lasting for more than a few weeks, continuing at night or with other unusual features, should prompt early imaging studies. The development of a visible mass or swelling follows pain in majority of patients. In ES of the pelvis, chest wall and the femur bone (most common sites of ES), mass may be indiscernible for a long time. Tumors of the vertebral compartment may present with symptoms of spinal cord compression, requiring urgent surgical and medical interventions.

The duration of symptoms before definitive diagnosis has been reported to be weeks to months, with a median of 3–9 months [33, 34]. Although, in a recent prospective study on a large cohort of patients, the duration to diagnosis did not affect survival in ES patients [35].

There are no blood, serum or urine tests that can specifically identify ES. Serum lactate dehydrogenase (LDH) may correlate with the tumor burden and hence prognosis.

About 85% of ES arise in the bones and in contrast to osteosarcoma, the flat bones of axial skeleton are more commonly affected [31]. In the long bones, ES classically arises from the diaphysis. Presentation with metastases (most commonly lungs, bone and bone marrow) occurs in up to 25% of patients. Metastases to lymph nodes, liver and brain are highly uncommon at presentation.

The initial investigation recommended is a radiograph in two planes, demonstrating osteolysis, periosteal elevation (Codman's triangle), wide zone of transition and a diaphyseal location. Magnetic resonance imaging (MRI) is superior (but may be more difficult logistically) to computerized tomography (CT) scans in delineating the relation to adjacent structures like nerves and vessels and the intramedullary extent of tumor, in addition to detection of skip lesions, all of which are crucial for local therapy planning. For the same reasons, imaging should include the entire bone and the joints proximal and distal to the lesion [32, 36–38]. All imaging should be done before any invasive intervention like biopsy.

The diagnosis of ES (or any bone malignancy) should never be ascertained without a biopsy. Incisional biopsy (core needle or open) should give adequate tissue for morphology, immunohistochemistry and molecular diagnosis and be considered to provide tissue for bio-banking for future translational research [39]. It is strongly recommended that initial biopsy be performed by the same surgeon who will later perform definitive resection of the tumor. This is to ensure that the biopsy tract can be excised in the final planned excision [40]. The soft tissue component (in the periphery of the tumor) in most bone malignancies is the ideal target for diagnostic biopsies, and deep sampling is not necessary. Diagnostic accuracy of core needle biopsies exceeds 95% and are superior to fine needle biopsy, which may not give sufficient material for cytogenetics, flow cytometry or gene profiling, when necessary [41].

The staging of ES entails looking for metastases in lungs, bones and bone marrow. A CT scan of the chest is mandatory to detect lung and pleural-based metastases. Conventionally, 99m-technetium whole-body radionuclide bone scans are used for detecting bony lesions, but fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) has been demonstrated to be highly sensitive for picking up bone metastases, may be even more than whole-body MRI [42]. Bone marrow metastases (present in less than 10% patients at presentation) are conventionally detected by biopsies from both posterior superior iliac crests. Care needs to be taken to avoid inadvertent biopsies from the primary tumor of pelvic origin when looking for bone marrow involvement. An FDG-PET CT scan (including chest CT) is a one-stop staging investigation for lung, bone and bone marrow metastases, gaining evidence that will obviate the need for separate bone scan and invasive (painful) bone marrow biopsies. The detection of micro-metastases in bone marrow or of circulating tumor cells in absence of overt metastases is currently under evaluation in prospective studies for its prognostic significance and possible therapeutic interventions [43].

5 Treatment Philosophy for Ewing Sarcoma

ES is a systemic disease, even when overtly localized, requiring systemic therapy in addition to local treatment of the tumor. This is historically evident when more than 90% of ES patients died due to systemic metastases, with only surgery or radiation of the primary tumor [44]. Among the first-known solid tumors to demonstrate chemosensitivity in the 1960s, the evolution of multiagent chemotherapy, sequential learnings and gains in survival with optimization of various combinations, by multi-institute, multinational, co-operative group clinical trials, is exemplary. With the use of multimodality therapeutic regimens including multiagent chemotherapy, surgery and radiation therapy (RT), majority of patients with ES can be cured (localized ES—~75%, metastatic 10–40%) [45].

6 Evolution of Chemotherapy for Localized Ewing Sarcoma

Demonstration of chemosensitivity of ES to single agents (cyclophosphamide, actinomycin D, doxorubicin and ifosfamide) in the 1960s was followed by the advent of multiagent chemotherapy in the 1970s. Traditionally the transatlantic groups (North America and Europe) have approached similar questions with similar results with minor variations in philosophies. Table 2 shows the sequential chemotherapy trials over last 5 decades, their major results and the lessons learnt.

To summarize, the addition of doxorubicin and realization of the importance of early dose intensification characterizes the major gains in survival of patients with ES. The standard of care for the North American group remains the dose intense alternate VCD/IE backbone and the Europeans prefer the simultaneous VIDE-based chemotherapy regimens. Four to six courses of intensive chemotherapy is fol-

Table 2 Evolution of chemotherapy regimens in ES

Study	Reference	Therapy	Patients (*n*)	5-year EFS	Important lessons from the trial
Intergroup Ewing Sarcoma Study (IESS)					
IESS-I (1973–1978)	[46]	VAC	342	24%	
		VAC + whole lung irradiation		44%	Benefit of WLI
		VACD		60%	Definite benefit of addition of doxorubicin
IESS-II (1978–1982)	[47]	VACD – High dose	214	68%	
		VACD – Medium dose		48%	Benefit of aggressive cytoreduction and early doxorubicin dose intensity
INT-0091 (InterGroup POG + COG) (1988–1993)	[48]	VACD	200	54%	
		VACD + IE	198	69%	Addition of IE in localized disease improves survival but not in metastatic disease
Memorial Sloan Kettering Cancer Centre Studies (MSKCC)					
T2 (1970–1978)	[49]	VACD (adjuvant only)	20	75%	
P6 (1990–1995 and 1991–2001)	[50]	HD-CVD + IE	36 and 68	77% (2 years)	Dose intensification and good results in localized disease but no improvement in metastatic setting
St. Jude Studies					
ES-79 (1978–1986)	[51]	VACD	52	82% (<8 cm) 64% (>8 cm)	Tumor volume is an important prognostic factor
ES-92 (1992–1996)	[52]	VCDIE	34	78% (3 years)	Tumor size loses prognostic significance when treated with more aggressive chemotherapy
SFOP/France					
EW-88 (1988–1991)	[53]	VD + VD/VA	141	58%	Histological response to chemotherapy a better prognostic marker than tumor volume
United Kingdom's Children Cancer Study Group (UKCCSG)/ MRC Studies					
ET-1 (1978–1986)	[34]	VACD	120	41%	The most important prognostic factor was tumor site (extremities (52%) > axial (38%) > pelvic (12%))
ET-2 (1987–1993)	[54]	VAID	201	62%	High-dose alkylating agents improved survival
Cooperative Ewing Sarcoma Study Group (CESS)					
CESS-81 (1981–1985)	[55]	VACD	93		Prognostic significance of tumor volume (100 ml: 80% vs. 31%) and histologic response to chemotherapy (90%: 79% vs. 31%)
CESS-86 (1986–1991)	[56]	VACD (SR) VAID (HR)	301	52% (SR), 51% (HR)	Same as CESS-81 and addition of Ifosfamide (high dose) may improve outcomes in HR
CESS + UKCCSG – EI-CESS					
EI-CESS-92 (1992–1999)	[31]	VAID/VACD (SR)	155	68%/61%	Prognostic significance of stage, histologic response, type of local therapy
		VAID/EVAID (HR)	326	51%/61%	
AEWS-0031 (2001–2005)	[57]	VCD/IE + GCSF (standard vs. interval compressed)	587	65% vs. 73%	Interval compression is possible without increasing toxicities and improves outcome
Euro-Ewing 99					
1999–2006	[58]	Impact of EWS gene rearrangement	565		EWS/ETS fusion type is nonprognostic
1999–2005	[59]	Primary disseminated ES	281	3-year EFS 27% and OS 34%	Age, site of metastases and tumor volume-based risk score may help prognosticate and decide treatment intensity

Table 2 (continued)

Study	Reference	Therapy	Patients (*n*)	5-year EFS	Important lessons from the trial
2000–2010	[60]	VAC vs. VAI in good-risk ES (<10% viable tumor postchemotherapy and volume <200 mL)	856	3-year EFS 75% vs. 78%	Ifosfamide and cyclophosphamide are interchangeable in good-risk ES
2000–2015	[61]	BuMel ABMT vs. VAI in localized high-risk ES (>10% viable tumor postchemotherapy or volume >200 mL)	240	8-year OS 64% vs. 55%	Localized high-risk ES may benefit from BuMel-based ABMT intensification
Euro-Ewing 2012					
2014–2019	[62]	Comparison of Transatlantic approaches, Alternate VCD/IE (2 weekly) vs. VIDE (3 weekly)	640	3-year EFS 67% vs. 61%	Dose-intensive VCD/IE is more effective, less toxic and has shorter duration for all stages of ES. The new standard of care

VAC Vincristine, actinomycin, cyclophosphamide, *VACD* VAC + doxorubicin, *IE* ifosfamide, etoposide, *HD* high dose, *SR* standard risk, *HR* high risk

lowed by local therapy and then adjuvant chemotherapy (8–10 courses). The recently published results of the randomized comparison of the two approaches, the Euro-Ewing 2012 trial, suggests better efficacy, lesser toxicity and shorter duration of treatment with the dose intensive regimen. The most important tumor and host-related prognostic factors are age, tumor volume, site and presence of metastases apart from histologic response to chemotherapy, which in addition to being prognostic, has recently been shown to be predictive in high risk ES, with treatment intensification with BuMel-based ABMT [53, 61].

7 Local Therapy in ES

Though the biggest gains in survival in ES can be attributable to chemotherapy, cure is not feasible without appropriate local therapy. With the demonstration of radio-sensitivity of ES, RT remained the standard local treatment modality for some decades, but with improvement in modern orthopedic surgeries, aiming preservation of function with sustained improvements in survivals, the choice of modality of local therapy in ES has evolved significantly [62]. To date, there have been no randomized trials for comparison of surgery and RT as local therapy modalities for ES and due to inherent biases and complicated moral and ethical dilemmas involved, such a trial may not be feasible in the future, too.

The planning of optimal modality of local therapy in ES necessitates multidisciplinary efforts from the beginning of treatment. The importance of interdisciplinary cross-talk between experts from various teams cannot be undermined and has demonstrated impact on outcomes in multiple recent clinical trials [63, 64]. The optimal local therapy of ES should be individualized based on patient's age, site and size of tumor, relationship to surrounding vital anatomical structures, aiming at organ and function preservation without compromising disease control.

Surgery in ES aims at a complete, en-bloc resection of tumor with adequate margins. Preoperative RT has traditionally been used for patients with local disease progression during chemotherapy but more recently it has been considered to avoid an intralesional resection. The local failure rates are comparable between this approach and for those with negative margin surgery in more amenable lesions [62].

The choice of reconstructive options includes autologous bone grafts, structural bone allografts and metallic endoprosthetics. Further elucidation about individual procedures is essential, but beyond the scope of this chapter. Special considerations should also be recommended in a skeletally immature child, with long-term growth and functional outcomes in mind. With advances in imaging modalities, surgical techniques and engineering innovations, the necessity for amputation in an ES patient would arise in scarce minority (<5–8%) of cases. Pathological fracture and neurovascular involvement may make limb salvage difficult but are not absolute contraindications [65].

Patients receiving definitive RT as the only local therapy modality usually represent an inherently unfavorable group with either tumors in sites not amenable to surgery (e.g., vertebrae) or with large volumes (independent poor prognostic factor). Definitive RT should be recommended for tumors where organ and function preserving surgery is not feasible or would be associated with significant morbidity. It is also recommended for patients with tumors where only an intralesional resection is feasible. Such debulking surgeries result in inferior disease control and necessitates adjuvant RT and thus adding to treatment-related morbidity. Both Cooperative Ewing Sarcoma Study (CESS) and European Intergroup - CESS (EI-CESS) trials confirmed that local control rates were similar in patients with an intralesional resection followed by RT as compared to those with definitive RT [62]. The indications for postoperative radiotherapy include positive surgical margins, poor histologic response to chemotherapy, large soft tissue component, pretreatment pathological fracture and contamination of surrounding normal tissue due to inadequate surgery [66]. The comparison of outcomes of ES patients between the UK Children's Cancer and Leukaemia Group (CCLG) and German Pediatric Oncology and Hematology Group (including Austria, Switzerland and Netherlands) (GPOH) treated in EICESS-92 clinical trial showed a significant impact of the choice of local therapy modality (14% higher local recurrence rate in the CCLG group). The analysis underscored the preferential "over-use" of RT (preoperative or postoperative, as per the treating physician's discretion) in the GPOH group as a major contributor for the better outcomes. Also, this benefit was more significant in the group of patients given postoperative RT due to residual viable tumor >10% than in those whom postoperative RT was given due to marginal or intralesional resections [67].

The St. Jude's Children Research Hospital experience with lower than 40 Gy radiation dose showed higher local recurrence rates [68]. For definitive RT, the recommended dose is between 55 and 60 Gy. Higher doses of RT with conventional fractionation of 1.8–2.0 Gy/ fraction have been tried with encouraging results and the long-term outcomes are awaited. Hyperfractionated RT did not result in improved local control or significantly reduced toxicity. For postoperative RT, doses of 45–50 Gy respectively is recommended based on a negative or positive surgical resection margin. The Pediatric Oncology Group (POG) randomized trial (POG #8346), laid the basis for the concept of "Tailored Portals" for RT in ES. The radiation of the tumor and an additional safety margin sufficed for equivalent local control rates in this randomized trial with that of radiation to entire tumor bearing compartment, resulting in significant reduction in toxicity [69]. In cavitary lesions like pelvis and thorax, targeting the residual tumor volume post chemotherapy may be adequate. Modern RT techniques like 3-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) have allowed significant sparing of normal tissues thereby reducing the possibilities of long-term adverse effects of RT. Technologies like proton beam therapy could further reduce adverse effects of RT and also allow RT dose escalation and improved local control.

8 Recurrent Ewing Sarcoma

Despite the insights gained and translated into the treatment of ES patients, around 20–30% of localized ES and 40–80% of metastatic ES patients will have recurrences. Early recurrences (within 2 years of initial diagnosis) and combined recurrences (local and metastatic) portend very poor further prognosis [70]. Although reports have suggested that local recurrence in ES almost always is followed by metastatic progression eventually [67]. ES shares the distinctive characteristic of other sarcomas, as opposed to other pediatric and adolescent tumors, that late and very late recurrences (up to 17.1 years after initial diagnosis) are also reported [71]. Hence, long-term continued monitoring and evaluations are recommended. The optimal modality of investigations for detection of recurrence is not supported by high level of evidence but a randomized trial of chest radiography versus CT scan of thorax and 3 monthly versus 6 monthly monitoring did not suggest an impact on survival after recurrence in bone malignancies [72].

Treatment after recurrence of ES is again multimodal with chemotherapy (topotecan, irinotecan, temozolomide, reuse of ifosfamide, cyclophosphamide and etoposide and sometimes with gemcitabine and docetaxel), surgical excision of all lesions, if feasible, and use of RT (definitive or adjuvant). The use of prolonged immunomodulatory metronomic maintenance therapy, has shown benefit in high-risk localized rhabdomyosarcoma in a recent report, may have a role in recurrent ES and is currently under investigation [73].

9 Ewing Sarcoma in the Adolescent and Young Adults (AYA)

The EI-CESS tumor registry showed that 56% of ES present in the second decade of life. Significantly more AYA ES presented with metastases, with larger tumor volumes and had poorer response to chemotherapy in this dataset [31]. The prognosis in the AYA ES patients has been historically shown to be poorer than in children. But more recent reports, when AYA ES patients under the age of 40 are treated with "pediatric like" aggressive protocols have abrogated these differences [56]. The factors that may impact the outcomes of AYA ES are described in Table 3.

ES could be considered a typical example of an AYA cancer, underlining the need for adaptation in understanding of unique biological and psychosocial distinctions and resultant requirements for this age group. The movements toward formation of a separate AYA Oncology Care Units in United Kingdom (Teenage Cancer Trust—www.teenagecancertrust.org), United States (Teen Cancer America—teencanceramerica.org) and Australia (CanTeen—www.canteen.org.au) are steps in the right direction for provision of specialized and optimal physical, medical, spiritual and psychologic space and care for AYA ES patients.

Table 3 Probable factors impacting outcomes of AYA ES

Type	Factors	Comments
Host-related factors		
	Growth spurts during adolescence	Possible implications on tumorigenesis and future therapies
	Hormonal changes during adolescence	Correlations not yet studied or adequately understood
	Comorbidities	Sports-related or physiological
	Pharmacokinetics	Decreased drug metabolism with increasing age as compared to children
	Pharmacodynamics	Increased toxicities with similar drug dose exposure (like peripheral neuropathy, cardiotoxicity)
	Compliance to treatment	Psychosocial impact on AYAs
	Adolescent behavior	Risk taking, ignoring symptoms, less amenable for referrals, peer pressures
Disease-related factors		
	More axial than appendicular location of tumors	Late presentations and less amenable to complete resections
	Larger volumes	Late presentations and requiring more intensive treatment modalities
	Different biology	Inherent chemotherapy resistance
Healthcare infrastructure-related factors		
	Lower enrollment in clinical trials	Less "disciplined" treatment compliance
	Treatment in inappropriate clinical setting	Adolescents being either treated in "pediatric" or "adult" units under respective protocols

Table 4 Potential long-term side effects in patients with ES

Group	Causative factors	Potential side effect	Comments
Cardiac	Doxorubicin Radiation to chest wall	Cardiomyopathy Early-onset metabolic syndrome	• Baseline and periodic cardiac function monitoring during treatment and later. • Limiting the dose of doxorubicin. • Using modulated radiation techniques and innovations. • Dexrazoxane administration. • Monitoring and correction with lifestyle modifications.
Gonadal	Alkylating agents Radiation	Sterility (predisposition in males)	• Adequate counseling at baseline. • Cryopreservation of sperms and ova (in post pubertal patients) before starting treatment. • Transposition of ovaries and testis (if in radiation field).
Musculoskeletal	Radiation Amputation Limb-sparing surgeries with prosthesis	Growth deficits Loss of limb and function Late prosthesis failure/ infections	• Consideration during planning of RT (see text). • Rehabilitation (physical, vocational and psychosocial). • Provision for continued follow-up and cost of continued care.
Second malignancies	Anthracyclines Alkylating agents Radiation	Acute leukemia Myelodysplasia Sarcoma in radiation field	• Limited scope for prevention. • Treatment as de-novo cancers.
Renal	Ifosfamide Cyclophosphamide Radiation to bladder/ kidneys	Renal tubular damage Bladder fibrosis	• Periodic relevant monitoring during treatment and prevention. • Bladder rehabilitation (if fibrosis).
Psychosocial	Adolescence Prolonged and intensive treatment Loss of limb/function Loss of educational/ vocational opportunities Peer pressures	Impact on treatment compliance and hence outcomes Loss of self-confidence Depression/anxiety	• Age-appropriate counseling before and during treatment and continued during follow-up. • Formation of social support groups for sarcoma survivors. • Creation of opportunities for educational / vocational rehabilitation for reintegration back into society as productive contributing members.

10 Long-Term Complications in Survivors of Ewing Sarcoma

Majority of patients with localized ES and substantial number of patients presenting even with metastases, will be cured of the disease and will be long-term survivors. The intensive treatment modalities used to achieve these cure rates may result in acute and late toxicities. Table 4 describes important considerations for prevention, monitoring and management of some of these long-term toxicities.

Optimization of appropriate treatment modalities used in the treatment of ES can help modulate (if not prevent) some of these potential long-term side effects and deserves adequate attention starting from initiation of treatment and continued during follow-up.

11 How We Do It at TMC

A suspected case of ES is advised a radiograph and MRI of the concerned region. A core needle biopsy establishes the diagnosis. PET-CT scan (including CT chest) is done for staging. Neo-Adjuvant chemotherapy (vincristine, ifosfamide, etoposide, cyclophosphamide and doxorubicin-based regimen) for 12–16 weeks is followed by local therapy. All patients after completion of neo-adjuvant chemotherapy are evaluated for feasibility of a surgical resection. For patients undergoing surgery, postoperative adjuvant radiation therapy is considered for positive/ close surgical margins or if histologic response is suboptimal, based on discussion in the multidisciplinary joint meeting. Patients with inoperable primary disease are considered for definitive RT. Adjuvant chemotherapy is continued as a maintenance for a total of 14–16 courses (dactinomycin replaces doxorubicin respecting cumulative dose limits).

Each decision point (planning of treatment, local therapy, palliation) is ideally discussed in multidisciplinary joint meeting. Financial, nutritional and psychosocial support is optimized based on need.

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Wilms Tumor

Badira Cheriyalinkal Parambil and Girish Chinnaswamy

Abbreviations

ACD	Dactinomycin
ADR	Doxorubicin
AVWS	Acquired Von Willebrand syndrome
BSA	Body surface area
COG	Children's Oncology Group
NCRP	National Cancer Registry program
RFS	Relapse-free survival
SIOP	International Society of Paediatric Oncology
SOS	Sinusoidal obstruction syndrome
VCR	Vincristine
VOD	Veno-occlusive disease
WT	Wilms tumor

1 Introduction

Wilms tumor (nephroblastoma), an embryonal neoplasm, accounts for approximately 90% of all pediatric renal tumors. It rarely occurs in adolescent or adults, accounting for less than 1% of all renal tumors [1]. Multidisciplinary approach in the treatment of this cancer has evolved over the decades through cooperative group studies and has shaped the current treatment strategies with outstanding results. The two largest collaborative groups that have studied the optimal management of Wilms tumor are the Children's Oncology Group (COG) and the International Society of Paediatric Oncology (SIOP). Substantial progress has been made by refining risk stratification and application of molecular information that helps in tailoring treatment to maximize cure with minimal late effects.

2 Epidemiology

The incidence of Wilms tumor (WT) is 7.1 cases per 1 million children younger than 15 years. Approximately 650 cases of WT are diagnosed in the United States and 80 cases in the UK each year [2]. Asians have a lower incidence of WT. As per the National Cancer Registry program (NCRP) report of hospital-based cancer registries (2007–2011), the proportion of childhood cancers relative to cancers in all age groups in India varied between 1.2% and 10.5%. Of these, renal tumors comprised 1.8%–4.8% in boys and 2.4 %–5.9% in girls in different registries [3]. The tumor is usually unilateral, but synchronous bilateral or multifocal tumors can be seen in approximately 5%–10% of patients. The male to female ratio is 0.92:1 in unilateral cases and 0.6:1 in bilateral cases. The mean age at diagnosis is 44 months in unilateral and 31 months in bilateral cases [4, 5]. An associated congenital malformation syndrome in seen in around 10% of WT patients [6].

3 Embryology and Pathology

The definitive fetal kidney develops from the ureteric bud forming collecting ducts and blastema, which subsequently forms the stroma and the rest of the tubular structures. The blastema usually disappears by 36 weeks gestation but is retained in 1% of infants where they are called "nephrogenic rests" that can be induced to form WT through acquisition of genetic mutations or epimutations. In 40% of unilateral and 90% of bilateral WT patients, these nephrogenic rests can be identified [7]. Nephroblastomatosis is defined as the "diffuse or multifocal presence of nephrogenic rests or their recognised derivatives."

Histologically, there are three main types of cells in the tumor: blastema, epithelial, and stroma (mesenchyme) (Fig. 1a). Histopathology is used across cooperative groups to assess risk. In COG protocols, which advocate upfront surgery, presence of anaplasia (diffuse and focal) is a high-

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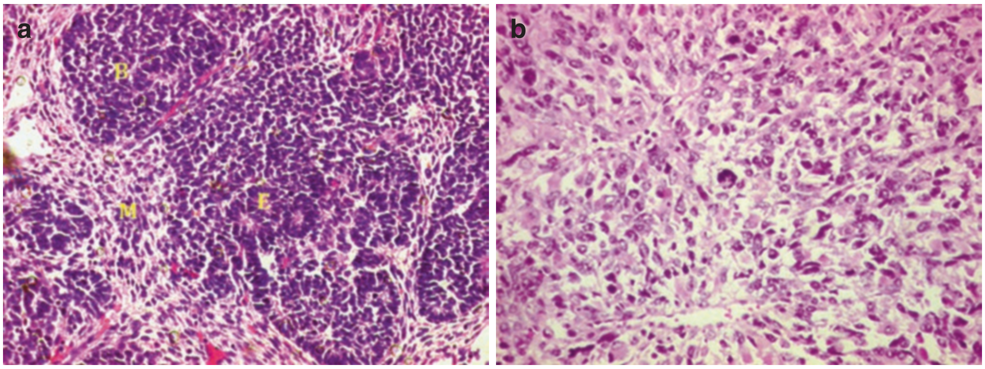


Fig. 1 (**a**) Triphasic Wilms tumor containing epithelial tubules (E), blastemal cells (B) and mesenchymal cells (M). Hematoxylin and eosin stain, 20×. (**b**) Microphotograph showing Wilms tumor with anaplasia. Enlarged, hyperchromatic nuclei are seen along with atypical mitotic figures. Haematoxylin and eosin stain, 20×

risk factor and in SIOP protocols, which recommend delayed surgery post neoadjuvant chemotherapy for 4–6 weeks, diffuse anaplasia and blastemal predominance is considered high risk and requires treatment modification. Anaplastic histology is seen in about 10% of WT and is considered the single most important histologic predictor of response and survival. The features of anaplasia include (a) hyperchromasia and (b) multipolar mitotic figures (Fig. 1b).

Any of the following situations on histopathology merits assignment to the "diffuse anaplasia" category:

1. Nonlocalized anaplastic change in the tumor specimen
2. Anaplastic change or nuclear unrest (nuclear or mitotic abnormalities that approach, but do not attain, the degree required for designation of anaplasia) in invasive sites or any extrarenal deposits
3. Localized anaplastic change in a tumor with severe nuclear unrest elsewhere
4. Anaplasia in a random biopsy specimen
5. Anaplasia involving the edge of one or more sections, and the site(s) from which the sections were taken cannot be determined.

If anaplasia is confined to one or more discrete areas, is not present in extrarenal sites, and cells outside of the anaplastic site show no features of nuclear unrest, it is considered "focal anaplasia."

4 Genetics and Epigenetics

Commonly mutated genes in WT are few, the discovery of which began with studying the constitutional predisposition syndromes of WT. Approximately one-third of WT cases involve mutations in WT1(11p13 locus), CTNNB1, or WTX [8]. A second WT gene; WT2 maps to 11p15 locus, and germline defects manifest as Beckwith–Wiedemann syndrome (BWS). BWS has different molecular mechanisms, and the overall tumor risk is between 5% and 10% [9]. Another 20% of WT cases results from mutations in miRNA processing genes (miRNAPG), including DROSHA, DGCR8, DICER1, and XPO5 [10]. Other recurrently mutated genes in WT include SIX1 and SIX2 (transcription factors that play key roles in early renal development) [10], EP300, CREBBP, and MYCN [11].

Table 1 Wilms tumor (WT) predisposition in genetic disorders

	Gene	Risk of developing WT
WAGR syndrome	WT1	50%
Denys-Drash syndrome	WT1	90%
Frasier syndrome	WT1	<5%
BWS—Overall risk	WT2	4.1%
• Loss of imprinting at ICR2	WT2	1–2%
• Gain of methylation at ICR1	WT2	22.8%
• Paternal 11p15 isodisomy	WT2	6.2%
Sporadic aniridia	WT1	50%
Isolated hemihyperplasia		5.9%

Around 30%–50% of mutations appear to converge on the process of transcriptional elongation in renal development and include the genes MLLT1, BCOR, MAP3K4, BRD7, and HDAC4 [11]. Anaplastic WT is characterized by the presence of TP53 mutations. The risk of developing WT in various genetic disorders is detailed in Table 1.

5 Clinical Presentation

Majority of patients present with an asymptomatic abdominal mass detected usually by the caregiver or by pediatrician during visit for unrelated reasons. Abdominal pain (mild in intensity, dull ache) is present in approximately 40% of children. Gross hematuria is observed in 18% of children (and 24% have microscopic hematuria). Hypertension, due to increased renin activity, is seen in about 25% of children which usually abates following nephrectomy [12]. Constitutional symptoms such as fever, anorexia, and weight loss are uncommon and seen in 10% of patients. Atypical presentations, seen in <10% of cases, are mostly due to vascular infiltration or compression of surrounding organs. These include vascular extension into renal vein or inferior vena cava, seen in 4% of patients which can present as hepatomegaly, limb edema, ascites, or even varicocele [12]. Occasionally, a child may present with acute abdomen with severe abdominal pain, tender mass, anemia, fever, and hemodynamic instability suggestive of tumor bleed or rupture, which may require emergency surgical intervention.

Acquired Von Willebrand syndrome (AVWS) type I or III is seen in about 1% to 8% of WT, due to complete absence of an inhibitor against VWF and responds to chemotherapy and/or tumor resection. Absorption of VWF multimers on to nephroblastoma cells resulting in a reduction of plasma levels of VWF [13] or hyaluronic acid produced by nephroblastoma cells may be the causative factor in atypical AVWS in WT, which may be associated with bleeding [12, 14, 15].

6 Evaluation and Workup

Baseline investigations to be done are as follows:

1. Physical examination should include
   (a) Blood pressure measurement
   (b) Nutritional status assessment
   (c) Examination of abdominal mass and liver
   (d) Looking for congenital anomalies and syndromic features especially overgrowth features, hemihypertrophy, aniridia, genitourinary anomalies, and any developmental delay
2. Complete hemogram
3. Biochemistry: liver and renal function tests
4. Coagulation tests, especially if AVWS is suspected
5. Ultrasound scan of abdomen: Done as an initial investigation to define the epicenter of the tumor, and it can also identify associated intravascular thrombus, liver metastasis, and associated genitourinary anomalies.
6. Contrast-enhanced CT scan of abdomen, pelvis, and chest: Confirms the renal origin of tumor, location in the kidney, size and laterality, presence of renal vein or IVC thrombus, abdominal lymphadenopathy, tumor rupture, infiltration of adjacent organs, and metastases to liver or lung (Fig. 2).

   In case of multifocal or diffuse lesions, MRI helps better to differentiate between tumorous lesions and nephroblastomatosis. They are usually homogenous with little contrast enhancement and retain the shape of the rests and so are lenticular in multifocal lesions or are seen as diffuse thickening.
7. In rare cases where intracardiac thrombus is detected, an echocardiogram should be done.
8. Fine-needle aspiration cytology/biopsy of the tumor: This may be done as per institutional practice and is not mandatory especially if upfront nephrectomy is contemplated. It should be considered in upfront inoperable cases to exclude non-WT cases and in unusual clinical presentations (older age, i.e., >5 years, urinary infection, sepsis, unusual radiological findings such as calcifications, voluminous adenopathies, renal parenchyma not visible, or totally extrarenal process). Needle biopsy should be by a retroperitoneal approach and image guided if possible.

Needle biopsy prior to preoperative chemotherapy is permitted but not considered standard practice according to the current SIOP protocol. Additionally, needle biopsy is not taken into account for staging purposes in SIOP protocols, which is solely determined based on nephrectomy specimen regardless of timing of the same. However, if a wedge or open biopsy is performed, the tumor gets upstaged to stage III. COG guidelines recommend upstaging to stage III if any biopsy (Trucut/needle or wedge) is done for diagnosis prior to starting therapy.

Biopsy is not required in bilateral renal tumors as diagnoses other than WT are very rare and biopsy rarely detects high-risk pathology such as anaplasia. Needle biopsy is contraindicated in children <6 months of age (where upfront surgery is advocated as chances of benign lesions like mesoblastic nephroma and non-WT lesions like rhabdoid tumor are high), and if there is suspicion of tumor rupture or bleed. Biopsy is also unlikely to benefit in pure cystic tumors where upfront surgery is recommended.

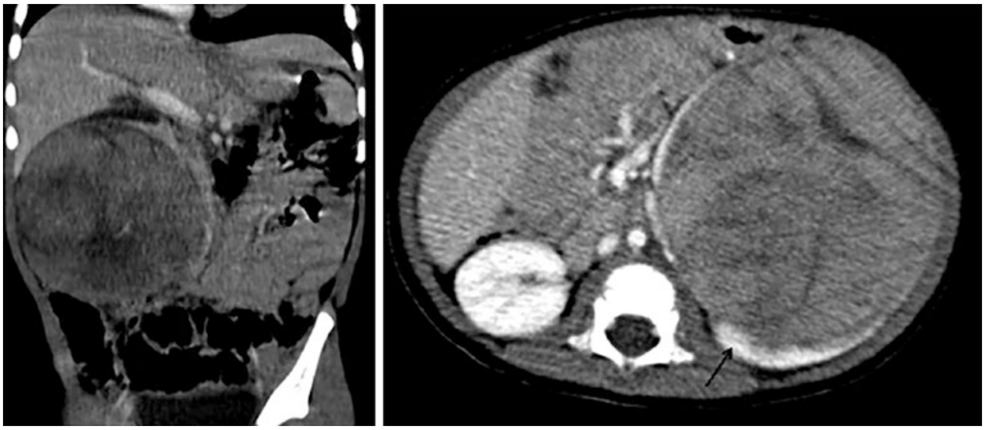


Fig. 2 Figure shows a well-defined lesion due to the formation of pseudocapsule with intrarenal origin indicated by the presence of 'claw' sign (shown by the black arrow on right side)

7 Principles of Management

The diagnosis and treatment of WT have evolved over the past decades though the collaborative efforts of the cooperative groups. The two largest collaborative groups that have contributed to the current treatment strategies are the COG (previous NWTS) and SIOP. A major difference in approach between the two groups is COG favors upfront surgery (nephrectomy), whereas SIOP favors preoperative chemotherapy followed by nephrectomy. There are several pros and cons highlighted for either of the two approaches as described in Table 2, but the outcomes have been comparable across both these approaches.

Histopathological assessment of tumor tissue helps in assessing risk type across both approaches though there are variations in same. Diffuse anaplasia is considered high risk across both groups. Risk categorization according to the groups is described in Table 3.

Table 2 Comparison between COG/NWTS and SIOP approaches to management of Wilms tumor

COG (Upfront Nephrectomy)	SIOP (Upfront Chemotherapy)
• Precise staging and pathology and, hence, accurate risk assessment • Fresh tissue available for molecular studies and research • Avoids unnecessary chemotherapy in case of benign lesions • Diagnosis of non-WT cases like rhabdoid tumor or clear cell sarcoma which warrants different chemotherapy is made early	• Reduces surgical complications like bleeding and tumor spillage • Decreases the use of doxorubicin and adjuvant radiotherapy by practically downstaging the tumor • Allows better surgical resection and reduces surgical morbidity • Renders an in vivo test of treatment response to NACT and tailors postoperative therapies, including identification of blastemal predominance, which requires high-risk therapy

Table 3 Risk categorization of Wilms tumor according to COG and SIOP

COG Classification (Upfront Surgery)	
Type	Histopathology Features
Favorable (FH)	No anaplasia
Unfavorable (UH)	Focal anaplasia Diffuse anaplasia
SIOP Classification (Upfront Chemotherapy)	
Risk	**Histopathology Features**
Low	Complete necrosis
Intermediate	Regressive (>66% necrosis) Epithelial predominant Stromal predominant Mixed type Focal anaplasia
High	Blastemal predominant (<66% necrosis with >2/3rd blastemal component) Diffuse anaplasia

7.1 Staging of Wilms Tumor

Staging is important in decision making, both for prognostication and therapeutic stratification of WT (Table 4). It is radiological- and surgico-pathological-based staging.

7.2 Treatment of Wilms Tumor

Wilms tumor treatment requires a multidisciplinary approach involving pediatric surgeon, pediatric radiation oncologist, pediatric oncologist, pathologist, and radiologist.

Table 4 Staging of Wilms tumor according to COG/NWTS and SIOP

Stage	Criteria
COG/NWTS Staging	
I	• Limited to kidney (without sinus vessel/capsule involvement) and completely resected AND • No tumor rupture AND No prior biopsy
II	• Extension beyond kidney but completely resected OR • Penetration of renal capsule OR • Invasion of renal sinus vessels
III	• Gross or microscopic residual tumor OR • Tumor spillage OR • Regional lymph node metastases OR • Positive peritoneal cytology OR • Transected tumor thrombus OR • Tumor rupture OR • Prior biopsy (wedge, FNAC or trucut)
IV	• Hematogenous metastases (lung, liver, bone, brain, etc.) OR • Lymph node metastases outside the abdomino-pelvic region
V	• Bilateral renal tumors at diagnosis
SIOP Staging	
I	• Limited to kidney (without sinus vessel/capsule involvement) and completely resected AND • No tumor rupture
II	• Extension beyond kidney but completely resected OR • Penetration of renal capsule OR • Invasion of renal sinus vessels/ vena cava but completely excised
III	• Gross or microscopic residual tumor OR • Tumor spillage OR • Regional lymph node metastases OR • Positive peritoneal cytology OR • Transected tumor thrombus OR • Tumor rupture OR • Tumor penetrating peritoneal surface/ tumor implant on peritoneal surface OR • Ureter transected OR • Tumor removed piecemeal OR • Wedge or open tumor biopsy prior to preoperative chemotherapy or surgery
IV	• Hematogenous metastases (lung, liver, bone, brain, etc.) OR • Lymph node metastases outside the abdomino-pelvic region
V	• Bilateral renal tumors at diagnosis

Historically, surgery alone was associated with 15%–20% 5-year survival across all stages that increased to 40%–50% with addition of radiotherapy. The introduction of chemotherapy improved survival to 60% with the addition of vincristine and dactinomycin which further increased to 70% with doxorubicin. The current survival rates of 90% are attributed to advances in surgery, pathology, radiology, and therapy. Integration of genetic and molecular information into risk stratification can further refine treatment, maximizing cure with minimal toxicity.

7.2.1 Surgery

Surgery remains mainstay in the treatment of WT though survival rates have improved with chemotherapy and radiotherapy. Radical nephrectomy with lymph node sampling via a transabdominal or thoracoabdominal incision, which allows thorough exploration of abdominal cavity, is the procedure of choice. Tumor removal should be complete and en bloc, without rupture because tumor spill has a sixfold increased risk of relapse [16].

Lymph nodes must be sampled and send for histopathological examination, even when not enlarged on clinical evaluation or radiology. This is required for accurate staging and subsequent treatment, as involvement of lymph nodes can lead to increased local recurrence and warrants administration of local radiotherapy [2, 12]. At least 5 LN stations are sampled including ineraortocaval LN to increase the likelihood of finding involvement [17]. These lymph node stations depends on the laterality of WT [18].

Renal-sparing surgery (partial nephrectomy or wedge resection) is recommended in children with bilateral WT, those predisposed to develop bilateral tumors (e.g., Denys-Drash or Frasier syndrome), and those with single/horseshoe kidney [19]. It is not recommended in standard unilateral tumors due to increased risk of tumor spill leading to recurrence and the relatively low risk of developing end-stage renal disease in long-term survivors of unilateral WT treated with nephrectomy [20].

COG advocates upfront surgery for WT, whereas SIOP advocates 4 and 6 weeks of chemotherapy for nonmetastatic and metastatic WT, respectively, with comparable survival outcomes, approaching 90% in localized and around 60%–70% in metastatic tumors at the population level. However, there are instances that may warrant preoperative chemotherapy in COG (bilateral WT, tumor thrombus in the inferior vena cava above the level of the hepatic veins, tumors invading surrounding organs with increased likelihood of surgical resection of vital organs, if surgical resection would result in excessive morbidity, or there is respiratory distress from extensive pulmonary metastases). Likewise, upfront surgery in SIOP is indicated in infants <6 months as benign causes like mesoblastic nephroma and non-WT causes like rhabdoid tumor are more likely and also when there is hemorrhage or tumor rupture with hemodynamic instability.

7.2.2 Chemotherapy

The three main drugs used in the treatment of WT are vincristine (VCR), dactinomycin (ACD), and doxorubicin (ADR) with cyclophosphamide, carboplatin, etoposide, and irinotecan added in high-risk cases with combinations varying as per protocol.

SIOP Approach: Preoperative Chemotherapy

As per SIOP protocol, two-drug (VCR+ACD) for nonmetastatic and three-drug (VCR+ACD+ADR) chemotherapy for metastatic WT patients are started soon after diagnosis. This preoperative chemotherapy is given for 4 weeks in case of nonmetastatic and 6 weeks in metastatic patients with reassessment for surgery done at 5th and 7th weeks, respectively.

Postoperative Chemotherapy

Post nephrectomy, the chemotherapy regimen is decided as per the risk stratification that takes into account staging and histopathology. The first dose of VCR following surgery should be given within 5–7 days of surgery, after assuring adequate bowel peristalsis, and no significant postoperative complications. Those who require radiotherapy should not have it delayed by >14 days post-surgery as delay can worsen outcomes. During radiation therapy, ACD and ADR are best avoided and can be given after a gap of 10–14 days in order to avoid excessive radiation toxicity. First subsequent dose of ACD after RT should be given at 50%. The postoperative chemotherapy is presented in Table 5.

Table 5 Postoperative chemotherapy [21–23]

Risk (histology-based)	Treatment		
	Stage I	Stage II	Stage III
Low risk	None	AV (27 weeks)	AV (27 weeks)
Intermediate risk[a]	AV (4 weeks)	AV (27 weeks)	AV (27 weeks) + flank RT[b]
High-risk blastemal predominant	AVD (27 weeks)	HR-1 (34 weeks)	HR-1 (34 weeks) + flank RT[b]
High-risk diffuse anaplasia	AVD (27 weeks)	HR-1 (34 weeks) + flank RT	HR-1 (34 weeks) + flank RT[b]

Abbreviations: A Actinomycin D, *D* Doxorubicin, *V* Vincristine, *HR-1* Etoposide, carboplatin, cyclophosphamide and doxorubicin

[a] Intermediate-risk, nonstromal, nonepithelial type with volume ≥ 500 mL was shown to have significantly improved outcomes when doxorubicin was added and hence in the SIOP-RTSG 2016 umbrella protocol same is advised [24]

[b] If there was diffuse tumor spill (outside of retroperitoneum),whole abdominal RT should be given

COG Approach: Adjuvant Chemotherapy

The COG protocol of chemotherapy for favorable histology WT, which risk stratifies based on staging, histology, molecular factors (LOH at 1p and 16q), after upfront radical nephrectomy, is shown in Table 6.

Table 6 COG protocol of chemotherapy for WT with favorable histology [25, 26]

Stage	LOH 1p & 16q	Risk Group	Treatment
Stage I <2 years, tumor ≤550 g	No	Very low risk	Nephrectomy and observation
Stage I	No	Low risk	EE4A—18 weeks
Stage I	Yes	Standard risk	DD4A—24 weeks
Stage II	No	Low risk	EE4A—18 weeks
Stage II	Yes	Standard risk	DD4A—24 weeks
Stage III	No	Standard risk	DD4A—24 weeks + RT
Stage III	Yes	High risk	Regimen M—31 weeks + RT
Stage IV lung (rapid responders)	No	Standard risk	DDR4—24 weeks + abdominal RT for local stage III, no lung bath
Stage IV	Yes	High risk	Regimen M—31 weeks + abdominal RT for local stage III + lung bath only for incomplete responders
Stage IV, non-lung metastases	No	High risk	Regimen M—31 weeks + abdominal RT for local stage III + RT to non lung metastases

EE4A, VCR + ACD; DD4A, VCR + ACD + ADR; Regimen M, VCR + ACD + ADR + Cyclophosphamide + etoposide

The protocol for unfavorable histology is more aggressive, with more intense chemotherapy and radiotherapy. It is depicted in Table 7.

Wilms Tumor with Pulmonary Metastases

Both the SIOP and COG protocols now are in agreement regarding radiotherapy in WT patients with pulmonary metastases in that if complete remission is attained, RT can be avoided though there is variation in the definition and scheduling of RT. The schema of approach to WT with pulmonary metastases is given in Fig. 3.

Table 7 COG protocol of chemotherapy for WT with unfavorable histology [23]

Stage	Focal Anaplasia	Diffuse Anaplasia
Stage I[a]	DD4A + RT	DD4A + RT
Stage II	DD4A + RT	Regimen UH-1 + RT[b]
Stage III	DD4A + RT	Regimen UH-1 + RT[b]
Stage IV	Regimen UH-1 + RT[b]	Regimen UH-2 + RT[b]

UH-1, VCR + ADR + cyclophosphamide + etoposide + carboplatin (revised UH-1 has lower cyclophosphamide dose); UH-2, VCR + ADR + cyclophosphamide + etoposide + carboplatin + irinotecan

[a] Stage I focal anaplasia on NWTS-5 was treated with two drugs (VCR + ACD) with lower outcomes compared to those who got 3 drugs (VCR + ACD + ADR) on retrospective analysis

[b] Stage II–III diffuse anaplasia and Stage IV focal anaplasia are currently given revised UH-1 chemotherapy to increase the outcomes on AREN0321 trial and if they have measurable disease post upfront surgery in stage IV diffuse anaplasia, they are offered UH-2

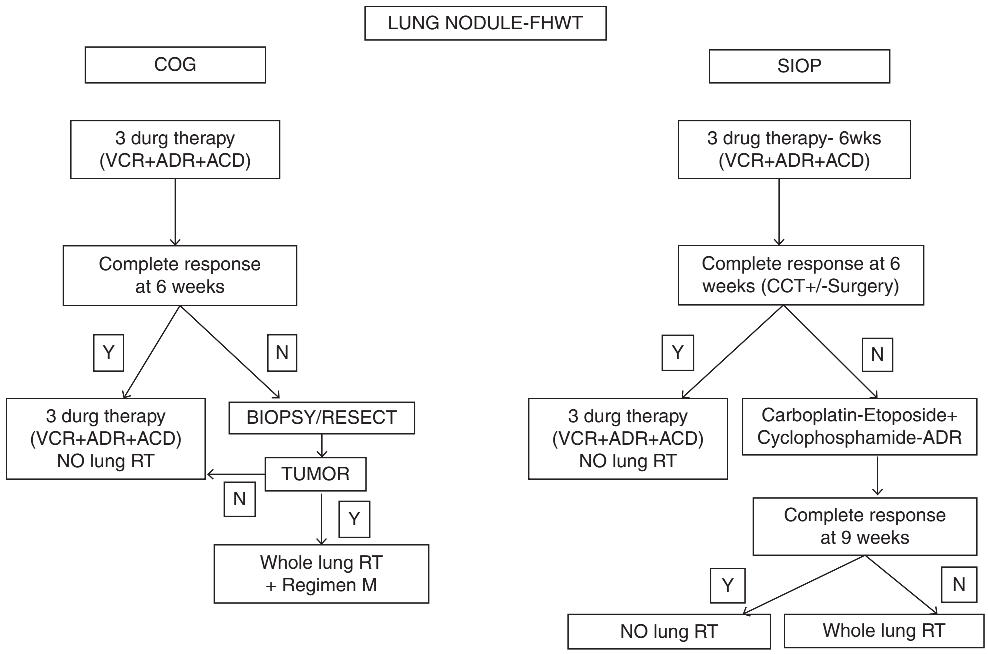

LUNG NODULE-FHWT
COG
3 durg therapy (VCR+ADR+ACD)
Complete response at 6 weeks
Y
N
3 durg therapy (VCR+ADR+ACD) NO lung RT
BIOPSY/RESECT
TUMOR
N
Y
Whole lung RT + Regimen M
SIOP
3 drug therapy- 6wks (VCR+ADR+ACD)
Complete response at 6 weeks (CCT+/-Surgery)
Y
N
3 durg therapy (VCR+ADR+ACD) NO lung RT
Carboplatin-Etoposide+ Cyclophosphamide-ADR
Complete response at 9 weeks
Y
N
NO lung RT
Whole lung RT

Fig. 3 The schema of approach to Wilms tumor with pulmonary metastases. FHWT, favorable histology Wilms tumor

Bilateral Wilms Tumor

Approximately 5% of all patients registered on NWTS-5 had bilateral WT [17] (Fig. 4). The risk of renal failure is a concern for patients with bilateral WT primarily secondary to loss of normal renal parenchyma due to bilateral nephrectomies (partial or complete) [12]. The incidence of end-stage renal disease is approximately 15% at 15 years post-surgery [19]. The challenge is the preservation of renal function mainly through nephron-sparing surgery (NSS), which complies with attainment of surgical resection with negative margins. Majority are too large at presentation for upfront NSS, and there are attendant surgical risks of intraoperative bleeding and postoperative small bowel obstruction. Therefore, preoperative chemotherapy is advocated to reduce tumor burden and facilitate NSS in this group [16]. These tumors have a significantly increased risk of anaplastic histology when compared to unilateral sporadic tumors; however, this is incongruent between kidneys and are mostly not picked up on initial biopsy if performed. Taking into account the above concerns in bilateral WT, management requires careful decision making with regard to chemotherapy, timing of surgery the type of surgery, and postoperative supportive care.

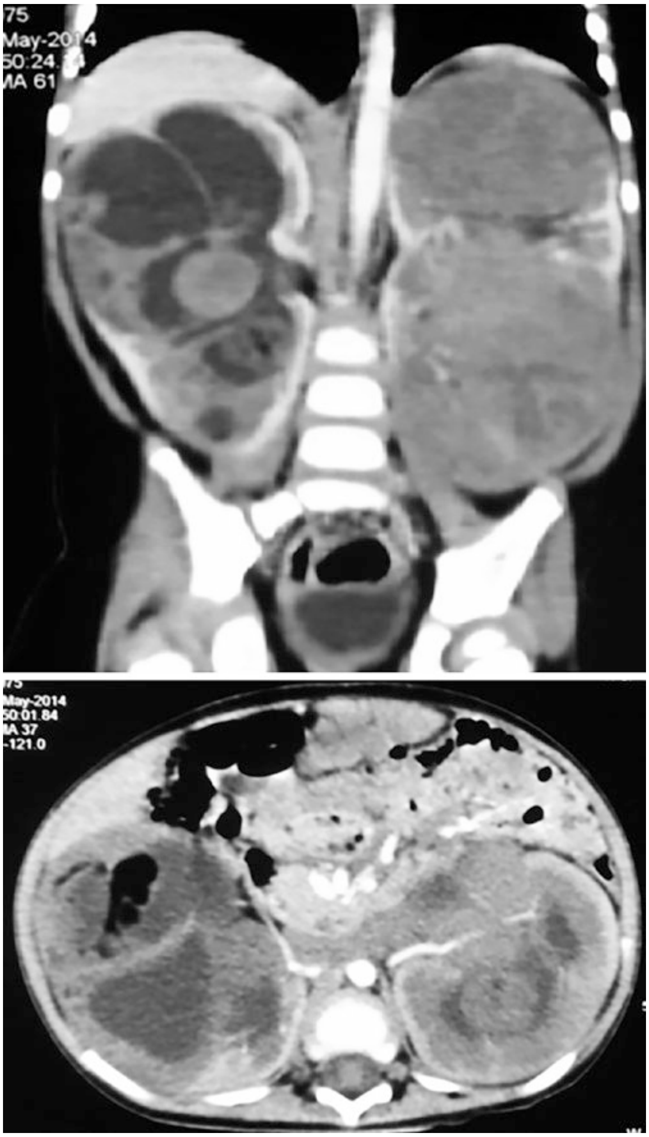


Fig. 4 Contrast-enhanced CT scan: coronal and axial images of bilateral Wilms tumor

There is current consensus between the COG and SIOP cooperative groups regarding the approach to bilateral WT. Upfront biopsy is not recommended if there are bilateral renal lesions. These children are given neo-adjuvant three-drug chemotherapy (VCR+ACD+ADR) and surgery done no later than 12 weeks, with first reassessment after 6 weeks. Review of data from St. Jude Children's Research Hospital showed that in bilateral WT, relapse was less when three-drug chemotherapy as described was used (8%) in comparison to two-drug preoperative chemotherapy (48%) [27]. The COG schema for bilateral WT (AREN0534) is presented in Fig. 5 [28].

Postoperative chemotherapy is based on histology using SIOP classification, as shown in Fig. 6.

Flank/abdominal radiotherapy is as per the local staging of WT. SIOP also initiates two-drug chemotherapy preoperatively for bilateral nonmetastatic WT (doxorubicin in metastatic and certain special cases for reinforcement) followed by surgery no later than 12 weeks and postoperative chemotherapy as per histology (described previously).

7.3 Radiotherapy

Radiotherapy should be started within 14 days of surgery unless there is a contraindication. COG and SIOP have different doses for various stages as depicted in Table 8.

7.4 Tackling Special Situations

7.4.1 Nephroblastomatosis

This can present unilaterally or bilaterally as multifocal or diffuse nephrogenic rests (NR) including the diffuse hyperplastic nephroblastomatosis with expansion of renal cortical tissue. The rests can be peri-lobar (PLNR), seen more in association with Beckwith-Wiedemann syndrome and hemihypertrophy or it can be intra-lobar (ILNR), seen more in the setting of WAGR and Denys-Drash syndrome [29]. SIOP recommends they be treated with two-drug chemotherapy (VCR+ACD) for a total duration of 1 year. Ultrasonography/MRI is used for assessing the lesions at the various time points. If WT develops at any time, multimodality treatment is given as per the stage, and two-drug regimen is continued for a total 1 year. Surgery has to be done if there is stabilization or progression of lesions in spite of chemotherapy, if a

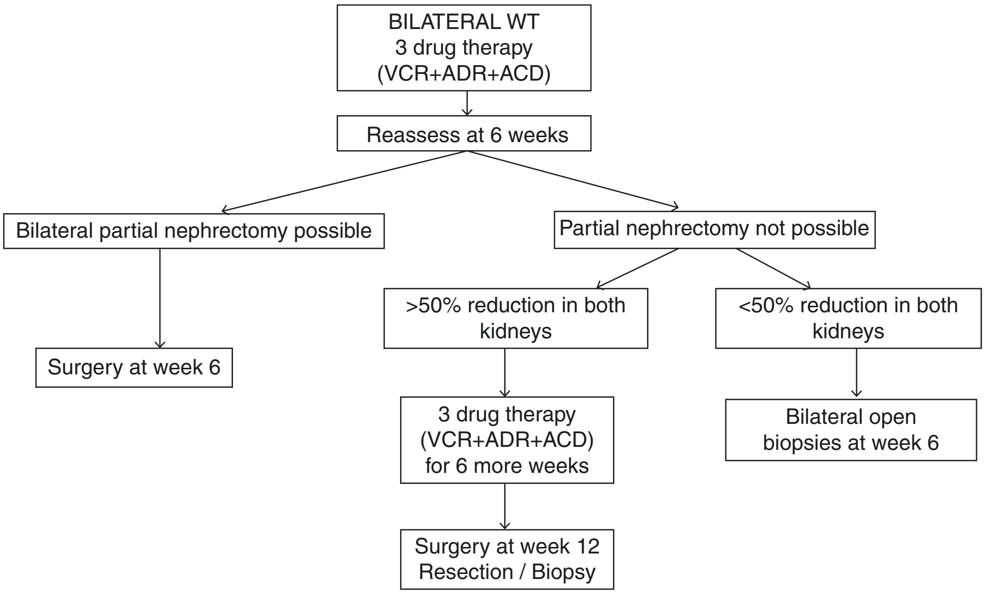

BILATERAL WT
3 drug therapy
(VCR+ADR+ACD)
Reassess at 6 weeks
Bilateral partial nephrectomy possible
Partial nephrectomy not possible
Surgery at week 6
>50% reduction in both kidneys
<50% reduction in both kidneys
3 drug therapy
(VCR+ADR+ACD)
for 6 more weeks
Bilateral open biopsies at week 6
Surgery at week 12
Resection / Biopsy

Fig. 5 COG schema for bilateral WT (AREN0534)

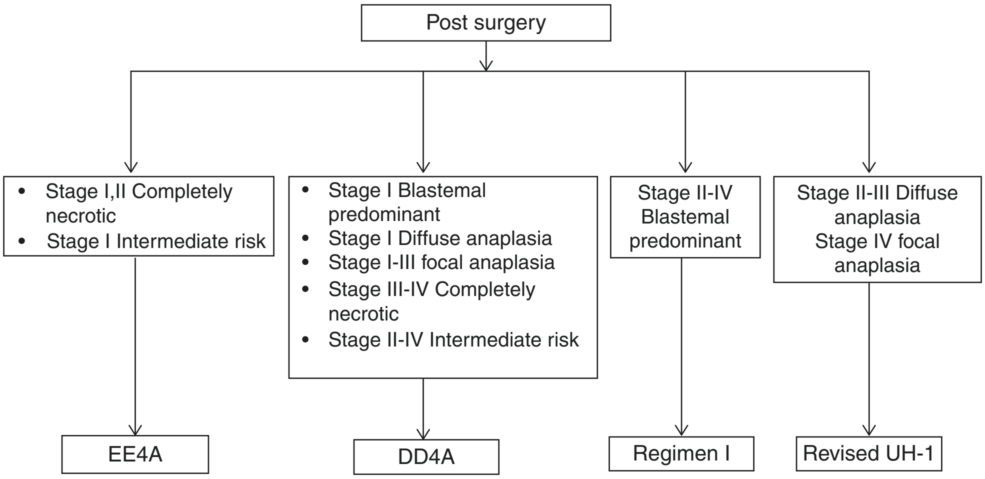

Post surgery
• Stage I,II Completely necrotic
• Stage I Intermediate risk
• Stage I Blastemal predominant
• Stage I Diffuse anaplasia
• Stage I-III focal anaplasia
• Stage III-IV Completely necrotic
• Stage II-IV Intermediate risk
Stage II-IV Blastemal predominant
Stage II-III Diffuse anaplasia
Stage IV focal anaplasia
EE4A
DD4A
Regimen I
Revised UH-1

Fig. 6 Post-operative chemotherapy based on histology using SIOP classification

nodular spherical lesion appears within the initial lesion or if the lesion becomes heterogeneous. Partial nephrectomy or wedge excision of the lesion should be done as in the case of bilateral WT.

7.4.2 Wilms Tumor with Tumor Thrombus

Preoperative chemotherapy with delayed surgical resection for intravascular thrombus is advocated by COG and SIOP. Upfront surgery is offered only for those patients with unstable thrombus likely to dislodge and cause acute symptoms (COG also does upfront nephrectomy for those with tumor thrombus in renal vein or infra-hepatic IVC). Although preoperative imaging usually delineates intravascular extension of the tumor, examination of the vena cava and renal vein should be done during surgery. A short renal vein thrombus may be resected along with the vein. Extension of thrombus to the infra-hepatic vena cava will require a vena cavotomy, after occluding the contralateral renal vein and cava above and below the thrombus. The thrombus should be removed and the venotomy closed. A longer thrombus (intra-hepatic, supra-hepatic, or right atrial) may require the assistance of a vascular or cardiac surgeon and cardiopulmonary by-pass. In cases with extensive caval wall infiltration, radiotherapy may be a better option as extensive surgery may not be able to achieve complete excision.

7.4.3 Inadequate Surgery

In developing countries, when upfront surgery of renal mass is done in peripheral hospitals, details are not available regarding tumor spill or lymph node sampling. The absence of node sampling may result in understaging and undertreatment of the tumor as reported by the NWTS group in 2005. Additionally, the pathological assessment of the tumor specimen is many a time inadequate leading to inappropriate risk stratification. Potentially, this could increase the risk of recurrence [2, 12]. An abstract presented in SIOP addresses

Table 8 Radiotherapy: indications and dose (COG and SIOP approach) [23]

Stage (COG)	Favorable Histology	Anaplastic Histology
I	No RT	10.8 Gy to tumor bed
II	No RT	10.8 Gy to tumor bed
III Tumor spill—localized —diffuse	10.8 Gy to tumor bed 10.8 Gy to flank 10.5 Gy to whole abdomen	19.8 Gy to tumor bed 19.8 Gy to flank 19.5 Gy to whole abdomen
IV	Local RT if Stage III + Address the metastases	Local RT if stage I-III + Address the metastases

Risk Group (SIOP)	**Treatment**		
	Stage I	**Stage II**	**Stage III**
Low risk	No RT	No RT	No RT
Intermediate risk	No RT	No RT	14.4 Gy(±10.8 Gy boost if residual)
High-risk blastemal predominant - Major rupture	No RT	No RT	25.2 Gy(±10.8 Gy boost if residual) 19.5 Gy
High-risk diffuse anaplasia —Major rupture	No RT	25.2 Gy	25.2 Gy(±10.8 Gy boost if residual) 19.5 Gy

RT to metastases:

Site	**Dose**
Liver—RT if lesions unresectable —If whole liver involved	25.2–39.6 Gy 19.8 Gy
Brain	Whole-brain RT to 21.6 Gy + boost of 10.8 Gy
Bone	25.2 Gy (Lesion + 3 cm margin)
Lymph node (if not surgically removed)	19.8 Gy

this very relevant issue in LMICs. In such cases, by giving three-drug chemotherapy in more than 100 patients, they have reported a 10-year DFS and OS of 84% and 89%, respectively, with acceptable toxicity [30]. So in such situations, three-drug chemotherapy with VCR+ACD+ADR without RT is a pragmatic approach.

7.4.4 Dosing in Infants

Initial NWTS studies showed that toxicity of chemotherapy was greater in infants [31]. Dosing based on body surface area (BSA) will deliver twice as much chemotherapy as dosing based on body weight. Also, metabolism of various drugs is immature in young infants. So chemotherapy should be weight based rather than BSA based. NWTS protocols recommend 50% dose reduction in infants [32].

7.4.5 Supportive Care

Hepatic Sinusoidal Obstruction Syndrome (SOS), Previously Known as Veno-occlusive Disease (VOD)

Child with SOS may present with abdominal pain, diarrhea, ascites, edema, tender hepatomegaly, and thrombocytopenia. The finding of portal hypertension or reversed portal venous flow on Doppler ultrasound is found only in advanced cases. The incidence was around 8% as defined by Seattle criteria in children treated under SIOP collaborative studies [33]. It typically develops after second to sixth dose of ACD, at 7–14 days after the last dose and resolves after a period of 6–180 days [33]. If SOS develops during preoperative chemotherapy, postoperative irradiation of large parts of the liver should be avoided. Acute episode should be managed with meticulous attention to fluid balance and restriction with diuretics when necessary. Patients with SOS should not be given ACD until the clinical findings and liver function normalize. During the first following course, patients should receive only 50% dose of ACD. If the symptoms reappear, this drug should be withdrawn permanently.

Cardiac Dysfunction

Children with WT on chemotherapy with doxorubicin should have echocardiography done at frequent intervals, after every 120 mg/m^2 of doxorubicin to detect any asymptomatic cardiac dysfunction. If ejection fraction is <50%, repeat echocardiography should be done prior to the next dose of doxorubicin and if normal to proceed with same. If it is still <50% or any time there is symptomatic cardiac dysfunction, doxorubicin should be withdrawn.

Hypertension

About 25% of children with WT have hypertension at presentation that can be treated with antihypertensives, especially angiotensin converting enzyme inhibitors. Calcium channel blockers may also be tried. Persistent hypertension usually responds to nephrectomy.

8 Molecular Prognostic Markers in Wilms Tumor

8.1 LOH 1p and 16q

NWTS-5 was prospectively designed to test the prognostic significance of LOH 1p and 16q across different stages of favorable histology WT [25], which showed that it was the most significant in prognostication after upfront surgery than either alone and was associated with a three-fold increased risk of relapse in Stage I/II tumors, which equated to relapse-free survival (RFS) of 75% versus 90% for those who had neither of these; for Stage III/IV, it was associated with a 2.5 times increased risk of relapse with RFS of 65% versus 83% for those with and without combined LOH 1p and 16q, respectively. The current AREN0532 and AREN0533 trials, which investigated intensifying therapy based on this, have shown improved outcomes. This molecular marker has not been found to be significant in studies that risk stratified based on post-chemotherapy histopathology as done in SIOP trials. However, combined LOH 1p and 16q is found only in 5% of newly diagnosed patients and <10% of relapsed cases.

8.2 1q Gain

Several studies have shown prognostic significance with respect to 1q gain across all stages in favorable histology WT. It is found in approximately 30% of newly diagnosed cases with a potential for risk stratification, influencing a significant proportion of patients and may be the driver mechanism in combined LOH 1p and 16q. In the COG study, which looked at the prognostic significance of 1q gain, the 8-year EFS and OS estimates were 77% and 88% for those with 1q gain and 90% and 96% for those without 1q gain [34], and in the presence of 1q gain, neither 1p and/or 16q loss was significant, though it retained significance in the absence of 1q gain.

8.3 TP53 Mutation

Diffuse anaplasia is recognized as high-risk histology across both COG and SIOP groups and is treated aggressively with chemotherapy and radiotherapy. However, recent analysis has identified TP53 mutations and/or 17 ploss in 62% of such cases and have found it to be associated with increased relapse and death when compared to those lacking TP53 abnormalities, which may further help to refine treatment in future [35].

8.4 11p15 Methylation

In AREN0532 studies, patients with very low risk WT (<2 years, stage I, FH, <550 g) with 11p15 LOH had an increased risk of relapse [AREN0532 Fall 2015 Final Study Progress Report].

9 Management of Relapse of Wilms Tumor

The two most important factors clearly associated with poor prognosis at relapse are anaplastic or SIOP high-risk histology and upfront doxorubicin use [36, 37]. They can be divided into the following [38]:

1. Standard-risk relapse (FH WT with prior VCR and/or ACD use)

   They benefit from doxorubicin, Etoposide and an alkylating agent (ifosfamide or cyclophosphamide) combined with radiotherapy.
2. High risk (FHWT with prior three or more drugs)

   The chemotherapy drugs commonly used are carboplatin, etoposide with either ifosfamide or cyclophosphamide. Topotecan has been added to the regimen to increase remission rates. High-dose chemotherapy with autologous stem cell rescue(ASCR) also may be tried. The studies seem to suggest a role for dose-intensive strategies to treat children with relapsing high-risk WT, although there is no consensus on whether or not high-dose chemo therapy with ASCR accounts for the improvement in post-relapse outcome compared with historical published data [38].
3. Very high risk (UHWT irrespective of prior chemotherapy)

   They have poor outcomes post recurrence despite use of intense chemotherapy and needs novel agents.

Surgery in recurrent WT has not been examined prospectively, but seems to improve outcomes if complete resection is possible, especially after chemoreduction, though it cannot be excluded that they had less aggressive disease [38]. SIOP-RTSG 2016 guidelines include considering resection after proven reduction of relapsed disease after chemotherapy. Applying radiotherapy to initially nonirradiated sites is uniformly accepted, but for previously irradiated sites, it is better done after detailed discussion with radiation oncologists [24].

10 Treatment Algorithms Used in Tata Memorial Hospital

Step 1 (Fig. 7)
Step 2A (Fig. 8)
Step 2B (Fig. 9)

Fig. 7 Wilms tumor treatment: upfront surgery versus delayed surgery, Tata Memorial Centre Guidelines

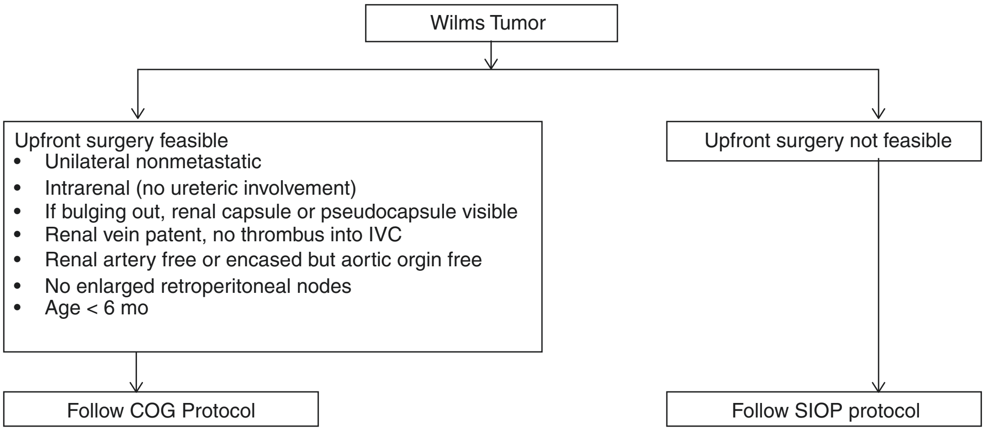

Wilms Tumor
Upfront surgery feasible
Unilateral nonmetastatic
Intrarenal (no ureteric involvement)
If bulging out, renal capsule or pseudocapsule visible
Renal vein patent, no thrombus into IVC
Renal artery free or encased but aortic orgin free
No enlarged retroperitoneal nodes
Age < 6 mo
Upfront surgery not feasible
Follow COG Protocol
Follow SIOP protocol

Fig. 8 Wilms tumor treatment following upfront surgery, Tata Memorial Centre Guidelines

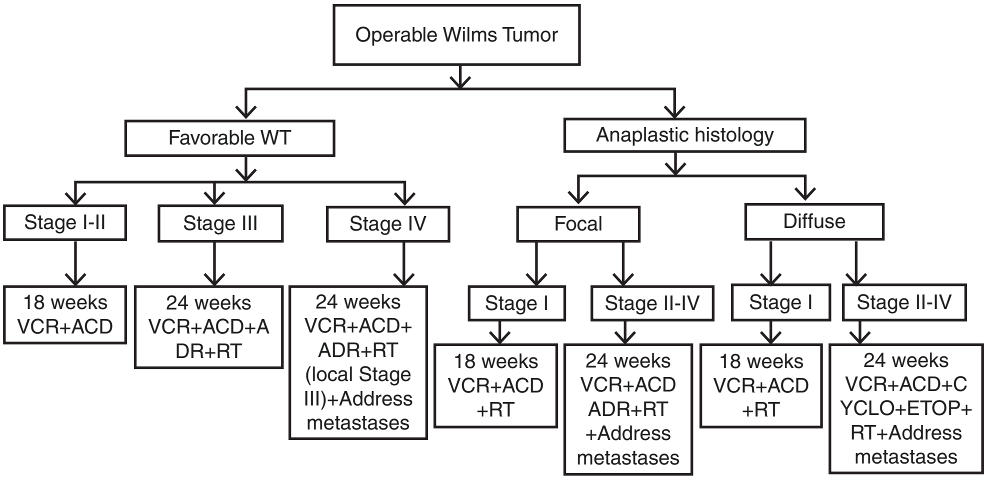
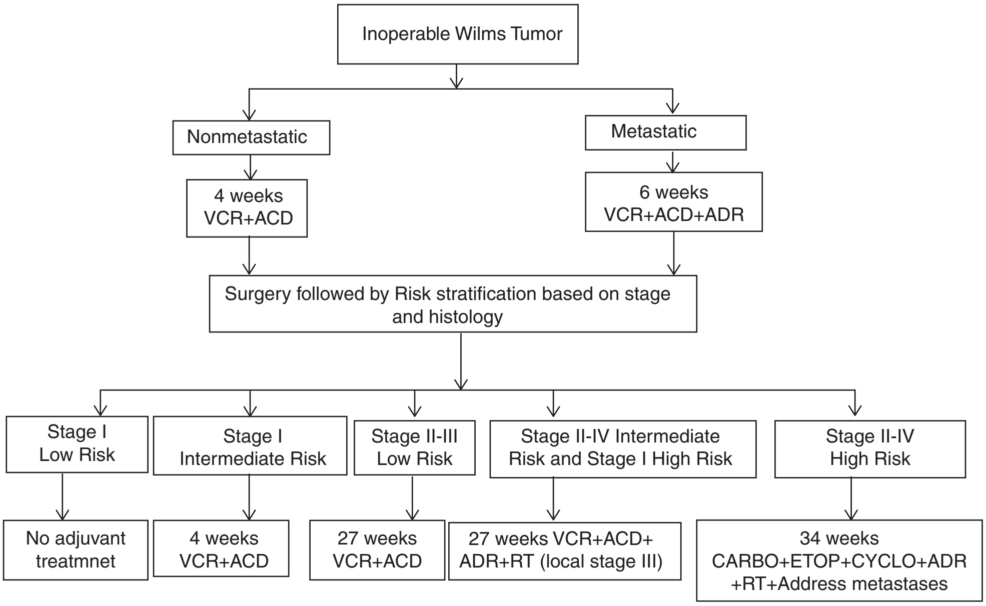

Operable Wilms Tumor
Favorable WT
Anaplastic histology
Stage I-II
Stage III
Stage IV
Focal
Diffuse
18 weeks VCR+ACD
24 weeks VCR+ACD+ADR+RT
24 weeks VCR+ACD+ ADR+RT (local Stage III)+Address metastases
Stage I
Stage II-IV
Stage I
Stage II-IV
18 weeks VCR+ACD +RT
24 weeks VCR+ACD ADR+RT +Address metastases
18 weeks VCR+ACD +RT
24 weeks VCR+ACD+CYCLO+ETOP+ RT+Address metastases

Fig. 9 Wilms tumor treatment for (upfront) inoperable tumors, Tata Memorial Hospital Guidelines


Inoperable Wilms Tumor
Nonmetastatic
Metastatic
4 weeks VCR+ACD
6 weeks VCR+ACD+ADR
Surgery followed by Risk stratification based on stage and histology
Stage I Low Risk
Stage I Intermediate Risk
Stage II-III Low Risk
Stage II-IV Intermediate Risk and Stage I High Risk
Stage II-IV High Risk
No adjuvant treatmnet
4 weeks VCR+ACD
27 weeks VCR+ACD
27 weeks VCR+ACD+ ADR+RT (local stage III)
34 weeks CARBO+ETOP+CYCLO+ADR +RT+Address metastases

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Neuroblastoma

Sajid S. Qureshi, Monica Bhagat, and Tushar Vora

Abbreviations

ACTH	Adrenocorticotropic hormone
ASCT	Autologous stem-cell transplantation
BuMel	Busulfan and melphalan
CEM	Carboplatin, etoposide and melphalan
CT	Computerized tomography
DFMO	Difluoro-methyl ornithine
EFS	Event-free survival
FISH	Fluorescence in situ hybridization
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GTR	Gross total resection
HVA	Homo vanillic acid
MIBG	Metaiodobenzylguanidine
MIS	Minimal access surgery
MKI	Mitotic karyorrhectic index
MRI	Magnetic resonance imaging
OMS	Opsomyoclonus syndrome
PET	Positron emission tomography
SCT	Stem-cell transplant
USG	Ultrasonography
VIP	Vasoactive intestinal peptide
VMA	Vanillyl mandelic acid

1 Introduction

Neuroblastoma is the most common childhood tumor in the adrenal glands and sympathetic ganglia formed from the neural crest. Its inexplicable behavior, from spontaneous regression in infants to metastatic aggression in older children, has always been at the core of ongoing research. The clinical presentation depends on the site and the presence of metastatic disease seen in approximately half of the patients at presentation. Over the last decade, significant progress in molecular pathology, staging, risk stratification and therapy has occurred.

2 Incidence and Epidemiology in India and Global

Neuroblastoma accounts for 10% of pediatric cancers in high-income countries [1]. However, it accounts for only 1–3% of cases in low and middle-income countries [2]. The Indian Council of Medical Research (ICMR), National Cancer Registry Program, reported an incidence of neuroblastoma of 2.4–7.5% across India [3]. At the Tata Memorial Hospital (TMH), Mumbai, neuroblastoma constitutes 20% of all extracranial, extraosseous solid tumors in children below 15 years of age [4]. The median age of diagnosis is 19 months, and more than 90% are diagnosed before 5 years of age. Environmental factors like prenatal smoking, vaginal infection and occupational exposure to certain chemicals have been associated with neuroblastoma, but no conclusive evidence exists [5].

Owing to the absence of any known risk factors, efforts were made initially for the primary prevention of this disease by screening. The assumption of neuroblastoma at birth led to mass-scale screening in Japan and later in North America and Europe [6–8]. An increase in the incidence of early-stage neuroblastoma followed without a contemporaneous decrease in the incidence of advanced-stage disease in the screened children. Essentially biologically favorable disease

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was identified by screening resulting in an overdiagnosing of some neuroblastoma that would have remained undiagnosed. The consequence included excessive diagnostic and therapeutic procedures with substantial psychological morbidity and mortality from therapy-related complications. Therefore, mass screening for neuroblastoma is not recommended [9, 10]. A familial predisposition is seen in 1–2%, and these children are diagnosed early at 9 months. They also tend to have multifocal or bilateral disease in about 20%. The siblings have a 6% risk of developing neuroblastoma [11]. Several germline mutations have been associated with familial neuroblastoma, including ALK gene mutations (75%), PHOX2B gene mutations and deletions at 1p36 or 11q14-23. Rarely, children with other cancer predisposition syndromes like neurofibromatosis type 1, Costello syndrome, Noonan syndrome, Li–Fraumeni syndrome and Beckwith–Wiedemann syndrome can be at increased risk of developing neuroblastoma [12].

3 Molecular Pathology

Based on clinical factors and biological features at diagnosis, children with neuroblastoma can be subdivided into a favorable and an unfavorable group [13].

- Low or intermediate-risk: These children are younger than 18 months and have a favorable prognosis, with survival rates exceeding 95%. These tumors frequently have gains of whole chromosomes and are hyperdiploid.
- High-risk: These children are older than 18 months and have an unfavorable prognosis, with less than 50% survival rates. They have metastatic disease, near diploid or near tetraploid, segmental chromosome abnormalities (gains or losses) and/or MYCN gene amplification.

The biological parameters that significantly influence overall outcomes include [14] the following:

Ploidy of Tumor Cell (DNA Content). Diploid DNA content significantly negatively impacts outcomes in children less than 18 months, while in older children, ploidy does not affect the outcomes.

Amplification of MYCN Oncogene. MYCN amplification is the first tumor-derived genetic marker with clinical and prognostic value. It is present in about 16–25% of cases of neuroblastoma and 40–50% of patients with high-risk neuroblastoma, show MYCN amplification [15]. It is strongly associated with rapid tumor progression and poor prognosis in patients of all ages with any stage of disease [16]. In addition, MYCN amplification is also linked with specific clinical and biological features. Adrenal primary tumors frequently are amplified than the primary thoracic tumors. There is a strong association between MYCN amplification and unfavorable histology, diploidy, high mitotic karyorrhectic index (MKI) and loss of heterozygosity at 1p. Although a four-fold copy increase using fluorescence in situ hybridization (FISH) is defined as MYCN amplification, a recent COG study showed a two- to four-fold increase (MYCN gain) associated with inferior outcomes compared to a less than two-fold increase in MYCN copy (wild type) [17].

Segmental Chromosomal Aberrations. Several segmental chromosomal alterations (SCA), including deletions of chromosomes 1p, 3p, 4p and 11q, and gains of chromosomes 1q, 2p and 17q, have been reported [18–21]. In children older than 12 months with unresectable neuroblastomas without metastases and infants with localized unresectable or metastatic neuroblastoma without MYCN gene amplification, SCA has a significant effect on event-free survival (EFS) and/or overall survival (OS) than children without SCA [20, 21]. SCA confers a higher risk of relapse and inferior outcome than numerical alterations. In an analysis of the INRG database, an SCA at chromosomes 1p, 11q and 17q noticed a higher risk of relapse and a poorer outcome in patients without MYCN gene amplification [19]. SCA is frequent in most high-risk tumors; however, its significance is not relevant. Recently, distal 6q losses and amplification of regions not encompassing the MYCN locus were associated with extremely low survival probability [22].

4 Clinical Presentation in India and Global

Neuroblastoma is a tumor of the sympathetic tissue; therefore, it can arise anywhere from the neck to the pelvis. Most neuroblastomas are seen in the abdomen, and the adrenal gland is the most frequent disease site. The symptoms vary as per the site of origin and could be an asymptomatic mass, symptoms due to the mass or metastatic disease or paraneoplastic symptoms. Large abdominal masses can cause bladder and bowel symptoms or impair venous return leading to bilateral lower limb edema (Fig. 1). Rarely renal vascular encasement and compression may lead to renin-mediated hypertension. Large thoracic tumors may cause mechanical obstruction and respiratory distress.

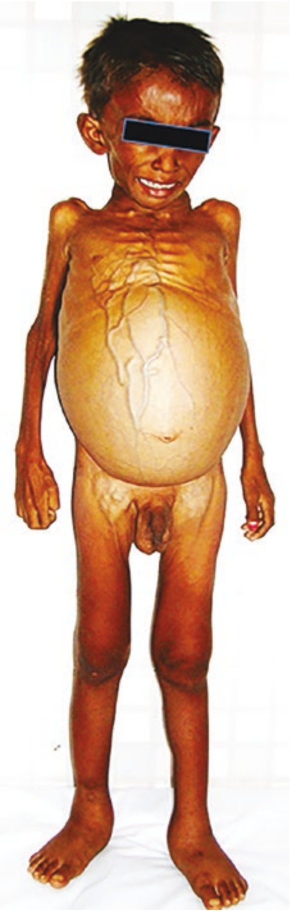

Fig. 1 Typical child with large abdominal neuroblastoma with dilated abdominal vein and bilateral pedal edema due to venous compression from the tumor mass. Extensive inguinal and cervical lymph node metastases is also present

Cervical and cervicothoracic lesions can produce Horner syndrome. Paraspinal tumors can extend into the neural foramina and may cause symptoms related to nerve roots and spinal cord compression. The metastatic disease typically presents as proptosis and periorbital ecchymoses (raccoon eye) due to tumor infiltration of the retrobulbar (Fig. 2). Extensive bone and bone marrow metastases cause bone pain, or pancytopenia leading to anemia, bleeding or infection. Massive liver metastasis, particularly in infants with stage 4S, may cause respiratory compromise, which could be fatal. Also seen in stage 4S disease is skin metastases presenting as bluish nontender subcutaneous nodules (mulberry nodule). Failure to thrive and fever may be seen with disseminated disease.

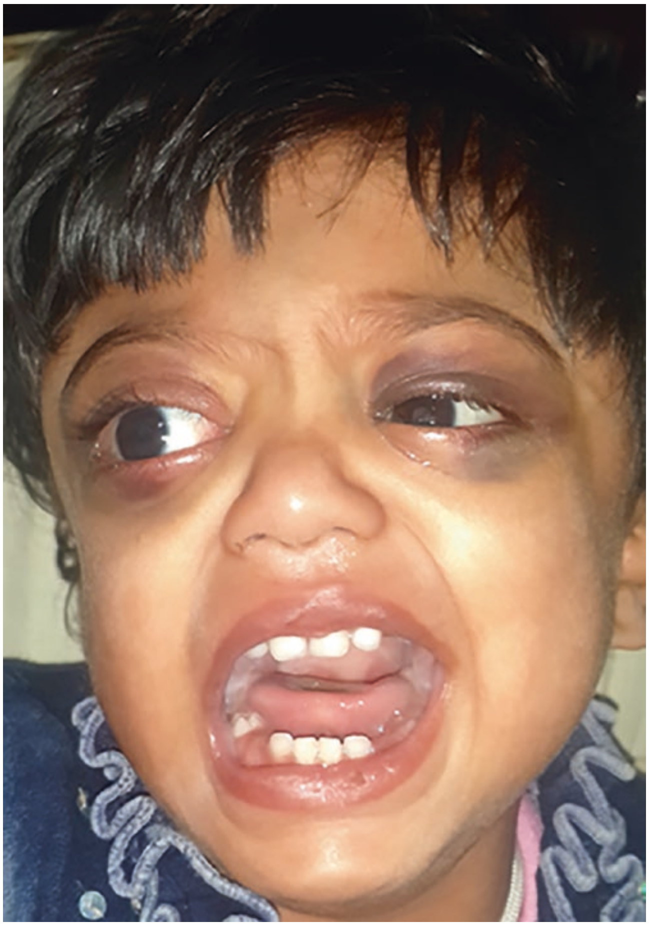

Fig. 2 Child with raccoon eye sign

5 Paraneoplastic Syndromes

Neuroblastoma is occasionally associated with paraneoplastic syndromes. Opsomyoclonus (Kinsbourne syndrome), a neurological paraneoplastic syndrome and diarrhea due to the vasoactive intestinal peptide (Kerner–Morrison syndrome), is a paraneoplastic hormonal syndrome associated with neuroblastoma.

5.1 Opsomyoclonus Syndrome (OMS)

Solomon and Chutorian gave the first association of this syndrome to neuroblastoma in 1968. It is seen in about 2–4% of newly diagnosed cases of neuroblastoma. The triad of opsoclonus (rapid and chaotic eye movements), myoclonus and ataxia and less frequent behavioral disturbances are noticed in these patients [23]. Pathogenesis seems to be an immunologic phenomenon wherein antibodies against neuroblastoma cells cross-react with neural cells in the cerebellum or elsewhere in the brain. Neuronal antibodies to Yo, Ri, Hu or amphiphysin may or may not be present, and antibodies can occur without a neurological syndrome. The treatment for OMS *per se* includes intravenous immunoglobulin, adrenocorticotropic hormone (ACTH) or corticosteroids, and Rituximab [24]. The underlying neuroblastoma in OMS is frequently associated with favorable biological features and has excellent survival rates [25]. Tumor resection certainly removes the antigenic stimulus and may improve the neurologic symptom, while chemotherapy could produce better results because of its immunosuppressive effects. Although likely with therapy, the neurological improvement may be a slow and partial or lifelong disability. Although the ideal Treatment varies, a combination of the different treatment approaches is undertaken. A randomized study of patients with OMS performed by the Children's Oncology Group (COG) showed an improved short-term neurologic response in patients treated with chemotherapy, corticosteroids and immunoglobulin, then without immunoglobulin [26].

5.2 VIP Syndrome (Kerner–Morrison Syndrome)

It is associated with increased vasoactive intestinal peptide (VIP) secretion, leading to watery diarrhea and hypokalemia. It is seen chiefly in mature tumors, and surgical excision usually leads to/results in the resolution of symptoms.

6 Evaluation and Work-Up

6.1 Tumor Markers

Urinary homo vanillic acid (HVA) and vanillyl mandelic acid (VMA) levels are raised in about 95% of neuroblastoma. They can be detected by either 24-hour urine collection or a spot urinary VMA level. These markers are additionally employed for monitoring response to therapy and surveillance for disease relapse following completion of Treatment [27].

Increased serum levels of ferritin and LDH signify disease burden. They have a potential for identifying a subgroup of high-risk patients with the poorest outcome, and this predictive strength can be exploited in low- and middle-income countries, where expert pathologic review may not be available, and resources may not exist to conduct genomic analysis of MYCN status and ploidy [28]. As a surrogate marker for identifying high-risk patients, the SIOP-PODC group has recommended serum ferritin ≥120 ng/mL and/or serum LDH ≥750 IU/L [29].

6.2 Bone Marrow Aspiration and Biopsy

Bilateral bone marrow aspirates and biopsies assess bone marrow to exclude bone marrow involvement. Immunohistochemical stains with neural-specific antibodies increase the sensitivity to at least 1 in 100,000 cells compared to 1 neuroblastic cell per 100 nucleated cells on light microscopy [30].

6.3 Radiology

Chest x-ray and ultrasound (USG) are routinely the initial investigations. Fine calcification may be seen in a plain x-ray of patients with large tumors. A contrast-enhanced computerized tomography (CT) scan is usually performed for all sites, while magnetic resonance imaging (MRI) is preferred for paraspinal disease with intraspinal extension (Fig. 3). The presence of specific features in radiology defined as image-defined risk factors (IDRF) is now used in the International Neuroblastoma Risk Group (INRG) Staging System for pretreatment risk stratification (Table 1). Twenty IDRFs have been identified based on the known locations of the primary tumor and the adjacent vital structures [31].

A skeletal survey for evaluation of bone metastases was performed previously; however, its utility is now restricted to confirming questionable bone metastases only. A technetium-99 bone scan is more sensitive for cortical bone metastasis.

Metaiodobenzylguanidine (MIBG) radionuclide scan is a precise and sensitive scan in neuroblastoma. It is the gold standard for diagnostic evaluation of neuroblastoma for both the primary tumor and sites of metastases [32]. Because ^{123}Iodine isotope is not available in India, ^{131}I-MIBG is used for diagnosis and therapy (Fig. 4). Semiquantitative scoring methods are available to evaluate the disease extent and assess response to Treatment which has prognostic value. The most common scoring methods are the Curie and the International Society of Paediatric Oncology Europe Neuroblastoma (SIOPEN). However, 10% of patients may have non-MIBG avid tumors [33]. Positron emission tomography (PET) with fluorine 18-fluorodeoxyglucose (see Fig. 4), though not as specific or sensitive as an MIBG scan, is preferred in patients with tumors that are not MIBG avid [34].

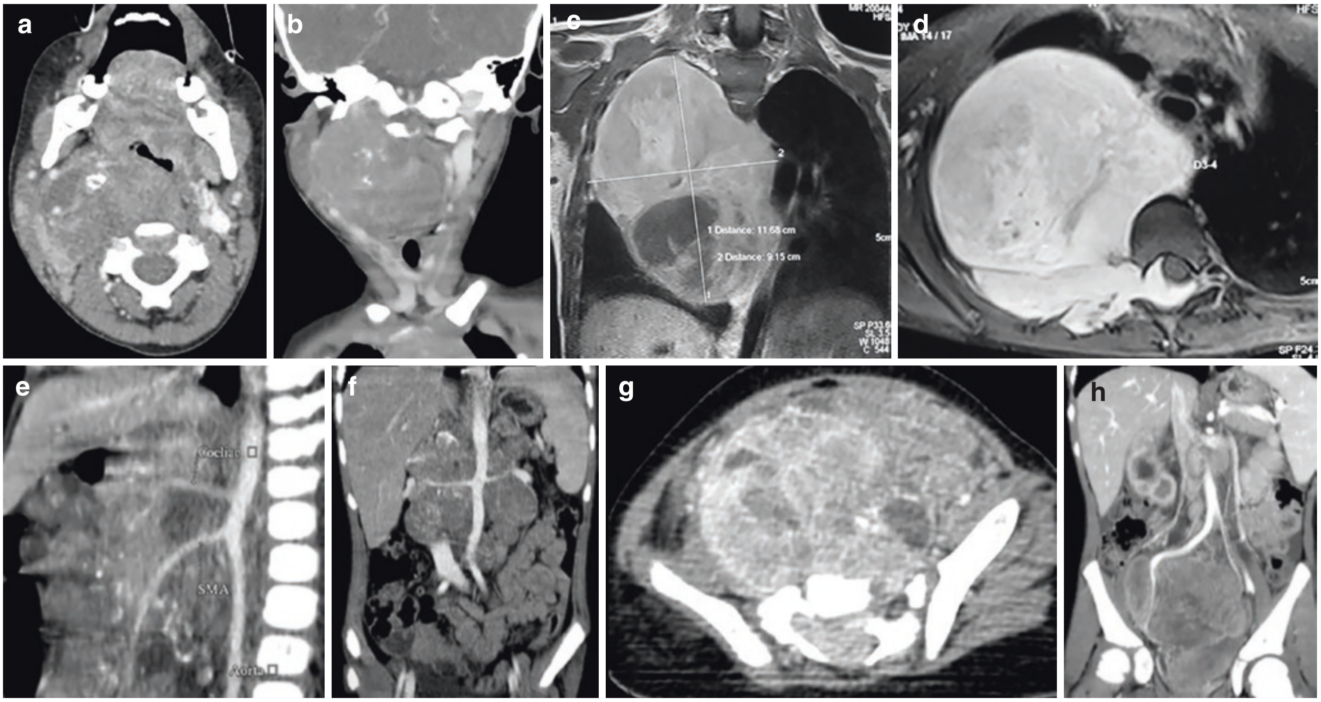

Fig. 3 Axial, coronal and sagittal computerized tomography images. (**a**, **b**) Cervical neuroblastoma with encasement of the carotid artery and compression of the airway. (**c**, **d**) Mediastinal neuroblastoma with more than one-third intraspinal extension. (**e**, **f**) Abdominal neuroblastoma with encasement of the coeliac, superior mesenteric and the renal arteries. (**g**, **h**) Pelvic neuroblastoma with intraspinal extension and encasement of the common iliac vessels

Table 1 Image-defined risk factors (IDRF) for neuroblastoma

Anatomic region	Description of IDRF
Multiple body compartments	Ipsilateral tumor extension within two body compartments (i.e., neck and chest, chest and abdomen or abdomen and pelvis)
Neck	Tumor encasing carotid artery, vertebral artery and/or internal jugular vein Tumor extending to skull base Tumor compressing trachea
Cervicothoracic junction	Tumor encasing brachial plexus roots Tumor encasing subclavian vessels, vertebral artery and/or carotid artery Tumor compressing trachea
Thorax	Tumor encasing aorta and/or major branches Tumor compressing trachea and/or principal bronchi Lower mediastinal tumor infiltrating costovertebral junction between T9 and T12 vertebral levels (because of risk of injury to anterior spinal artery)
Thoracoabdominal	Tumor encasing aorta and/or vena cava
Abdomen and pelvis	Tumor infiltrating porta hepatis and/or hepatoduodenal ligament Tumor encasing branches of superior mesenteric artery at mesenteric root Tumor encasing origin of celiac axis and/or origin of superior mesenteric artery Tumor invading one or both renal pedicles Tumor encasing aorta and/or vena cava Tumor encasing iliac vessels Pelvic tumor crossing sciatic notch
Intraspinal tumor extension	Intraspinal tumor extension (whatever the location) provided that more than one-third of spinal canal in axial plane is invaded, the perimedullary leptomeningeal spaces are not visible, or the spinal cord signal intensity is abnormal
Infiltration of adjacent organs and structures	Pericardium, diaphragm, kidney, liver, duodenopancreatic block and mesentery

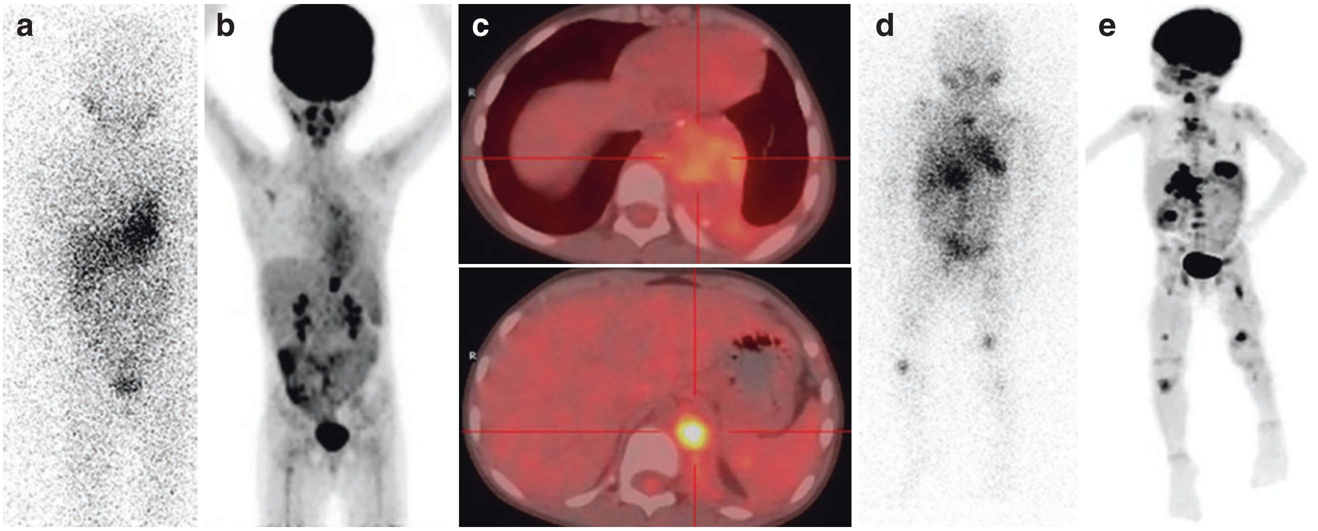

Fig. 4 ^{131}I-MIBG scintigraphy (**a**–**d**). Localized thoracoabdominal disease (**a**) and abdominal disease with skeletal metastases (**d**). Fluorine F 18-fluorodeoxyglucose-positron emission tomography scan (**b**, **c**, **e**). Same patients with localized (**b**, **c**) and disseminated (**e**) disease

6.4 Pathology

Neuroblastoma is a small round blue cell tumor of childhood with pathological features ranging from mature ganglioneuroma to less mature ganglioneuroblastoma to immature neuroblastoma with varying malignant potential. Histologically neuroblasts are small round cells with hyperchromatic nuclei almost filling up the entire cell. The neuritic process or neuropil is seen in most primitive neuroblasts. Homer-Wright pseudorosettes consisting of blue neuroblasts surrounding a central core of eosinophilic neuropil are also seen. Ganglioneuroma is composed of ganglion cells and Schwannian stroma, while ganglioneuroblastoma has features of both neuroblastoma and ganglioneuroma in varying proportions. Shimada et al. classified tumors as either favorable or unfavorable based on the patient's age and pathological features, including the presence or absence of Schwannian stroma, the degree of differentiation and the MKI [35].

6.5 Referrals Including Genetic Counseling

A family history of neuroblastoma, clinical features associated with mutations in predisposing genes, or elements suggesting predisposition such as bilateral or multifocal primary tumors qualify for genetic testing for mutations in neuroblastoma predisposition genes [36]. Surveillance with abdominal USG, urinary VMA and a chest radiograph should begin at birth or diagnosis of neuroblastoma predisposition and be continued every 3 months until 6 years of age, and then continued every 6 months until 10 years of age [36].

7 Staging

The International Neuroblastoma Staging System (INSS) staging for neuroblastoma was first described in 1986 and was a surgical staging system used by COG (Table 2) [37]. It could not be uniformly utilized on a larger platform for a clinical trial because it was all based on the surgeon's perception about the extent of resection. An alternative approach for presurgical staging based on clinical and biological features of the tumor and imaging was developed by the INRG task force in 2005. This has led to an INRG classification system and an INRG staging system [14, 38]. INRG has four subsets based on the presence and absence of IDRFs and metastatic status as LI, L2, M and MS. INRG stage MS is primary of any size/IDRFs with metastasis to liver, bone marrow or skin in children younger than 18 months (Tables 3 and 4 [14]).

Table 2 The International Neuroblastoma Staging System (INSS)

Stage/prognostic group	Description
Stage 1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (i.e., nodes attached to and removed with the primary tumor may be positive).
Stage 2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
Stage 2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement. The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs, except as defined for stage 4S.
Stage 4S	Localized primary tumor, as defined for stage 1, 2A or 2B, with dissemination limited to skin, liver and/or bone marrow (by definition limited to infants younger than 12 months). Marrow involvement should be minimal (i.e., <10% of total nucleated cells identified as malignant by bone biopsy or by bone marrow aspirate). More extensive bone marrow involvement would be considered stage 4 disease. The results of the MIBG scan, if performed, should be negative for disease in the bone marrow.

Table 3 International neuroblastoma risk group staging system

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of IDRFs and confined to one body compartment.
L2	Locoregional tumor with presence of one or more IDRFs.
M	Distant metastatic disease (except stage MS).
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver and/or bone marrow. The primary tumor can be INSS stage 1, 2 or 3.

IDRFs Image-defined risk factors

Table 4 International Neuroblastoma Risk Group (INRG) pretreatment classification [14]

INRG stage	Age (months)	Histologic category	Grade of tumor differentiation	MYCN	11q aberration	Ploidy	Pretreatment risk group
L1/L2		GN maturing, GNB intermixed					A (very low)
L1		Any, except GN maturing or GNB intermixed		NA			B (very low)
				Amplified			K (high)
L2	<18	Any, except GN maturing or GNB intermixed		NA	No		D (low)
					Yes		G (intermediate)
	≥18	GNB nodular neuroblastoma	Differentiating	NA	No		E (low)
					Yes		H (intermediate)
			Poorly differentiated or undifferentiated	NA			H (intermediate)
				Amplified			N (high)
M	<18			NA		Hyperdiploid	F (low)
	<12			NA		Diploid	I (intermediate)
	12 to <18			NA		Diploid	J (intermediate)
	<18			Amplified			O (high)
	≥18						P (high)
MS	<18			NA	No		C (very low)
					Yes		Q (high)
				Amplified			R (high)

GN Ganglioneuroma, *GNB* Ganglioneuroblastoma, *NA* Not amplified

8 Principles of Management

Neuroblastoma treatment includes observation or resection alone, restricted or substantial use of high-dose chemotherapy, including myeloablative therapy and stem-cell transplant (SCT), radiotherapy, isotretinoin and immunotherapy [39]. This wide availability of treatment options mandates a mechanism to identify patients who require no or high-intensity treatment. The tumor has been classified as low, intermediate or high risk in the earlier COG studies based on the INSS stage, age, International Neuroblastoma Pathologic Classification (INPC), ploidy, amplification of the MYCN oncogene, unbalanced 11q loss of heterozygosity and loss of heterozygosity for chromosome 1p [40]. With the introduction of the INRG classification system, the tumor has been classified as very low, low, intermediate or high risk based on INRG stage, age, histologic category, grade of tumor differentiation, MYCN amplification, 11q aberration and ploidy [14].

9 Surgical Management

Surgery plays a pivotal role in neuroblastoma treatment to accomplish local control of the disease. Due to the inherent tendency of these tumors for vascular encasement, resection can be a technical challenge [41]. The recognition of IDRF offers an actual appraisal of the complexity and the risk of surgical complications. Incomplete resection or surgical complications are typically seen in the presence of IDRF [42]. With due consideration to the IDRF, surgery can be considered in patients with L1 disease at presentation if necessary. All patients with L2 disease, especially high-risk diseases, should be considered for delayed surgery after chemotherapy. Irrespective of the primary disease site, adequate exposure for the surgical excision is paramount. This may range from minimal access surgery (MIS) to open exploration of two body compartments like a thoracoabdominal or cervicothoracic approach [43, 44]. Although very popular in general pediatric surgery, MIS is not always suitable for most neuroblastoma patients/presentations considering the complex relation to the vessels. However, for the small L1 disease, it may be appropriate in experienced hands, and MIS can even be utilized for obtaining biopsies. Complex sites like the cervicothoracic region require a cervicomanubriosternal approach or trapdoor approach [44]. The aim of surgery is complete safe surgical excision without sacrificing vital structures. However, this may not be feasible for most patients. Meticulous and persevering dissection safeguarding critical structures typically results in achieving the goal of safe resection [43]. The extent of surgery and the terminologies used to describe it are not uniform. Systemic failure in high-risk tumor neuroblastoma has prevented many from performing aggressive local surgeries; at the same time, extensive or unwanted surgeries have also been performed for low-risk diseases and tumors with intraspinal extensions. Complete resection with the removal of all visible and palpable macroscopic disease is usually called gross total resection (GTR). Incomplete resections have been variably defined as >95%, >90%, subtotal resections, etc., often on the intuitive assessment of the surgeon. Surgical complication rates have ranged from 5% to 25%. The frequent complications include vascular injury, prolonged intensive care stay, hemorrhage, nephrectomy, chylous leaks and neurologic deficits such as Horner syndrome and postoperative adhesions [44–46].

10 Medical Management

Essentially chemotherapy for neuroblastoma includes multiple rotating combinations of two or three drugs. The most common drugs used in various regimes include vincristine, etoposide, cisplatin, carboplatin, doxorubicin, cyclophosphamide, ifosfamide and topotecan [39]. Chemotherapy usually commences with multiple cycles as induction treatment with the primary purpose of reducing tumor burden, eliminating metastatic deposits if present, and rendering the tumor more amenable to surgical resection. Myeloablative therapy with carboplatin, etoposide and melphalan (CEM) regimen or busulfan and melphalan (BuMel) and autologous stem-cell transplantation (ASCT) is usually utilized for high-risk diseases [39]. Oral differentiation agent isotretinoin reduces the proliferation of neuroblastoma cells and induces differentiation after ASCT. Anti GD2 monoclonal antibodies after myeloablative therapy have improved the outcomes.

11 Radiation Management

The role of radiation has been limited due to various randomized trials, and its effect is variable in neuroblastoma. However, radiotherapy to the preoperative tumor bed after delayed surgical resection and ASCT is currently accepted as standard care for high-risk neuroblastoma. Radiotherapy is additionally used for spinal cord compression where chemotherapy does not improve symptomatically or in stage 4S, where enlarged liver with multiple metastases increases the abdominal pressure, and respiratory or renal compromise occurs. In the former, damage to the vertebrae may lead to scoliosis later in life. The use in unresectable or incompletely resected disease is not recommended currently. In the stage 4 disease with cortical bone metastasis, palliative doses for pain relief are given.

12 Metaiodobenzylguanidine (MIBG) Therapy

MIBG is an analog of the neurotransmitter norepinephrine. In their radioiodinated form, ^{131}I-MIBG and ^{123}I-MIBG are clinically used as tumor-targeted radiopharmaceuticals in diagnosing and treating neuroblastic tumors. ^{131}I-MIBG has a longer half-life than ^{123}I-MIBG, therefore, preferred in therapy. However, with variable results, MIBG therapy has been used only for refractory and relapsed neuroblastoma. For newly diagnosed high-risk neuroblastoma MIBG, Treatment is undergoing evaluation for use during induction therapy.

13 Risk-Wise Management Algorithms

13.1 Low-Risk Neuroblastoma

Observation or resection, chemotherapy restricted to symptomatic patients with low-risk biology can be offered for low-risk tumors [47]. Although surgery is preferred for L1 disease, observation alone is appropriate for asymptomatic infants with tumor volume less than 16 mL, even without a biopsy confirmation of the diagnosis [48]. After biopsy confirmation of favorable histology and MYCN nonamplification, other asymptomatic patients can also be offered a trial of observation [47–49]. Symptomatic patients can be provided limited chemotherapy to decrease tumor burden followed by a safe resection, preferably a gross total resection; however, even incomplete resection is acceptable for low-risk tumors [47]. Asymptomatic and favorable biology (MYCN nonamplified, no 11q aberration and hyperdiploid) stage 4S patients can also be observed given the excellent survival and spontaneous regression seen in 80% [47, 50]. Stage 4S patients with life-threatening symptoms frequently require intervention for multiple liver metastases causing hepatomegaly and raised abdominal pressure leading to respiratory compromise. Low-dose radiation (4.5–6 Gy in 3–4 fractions) to the liver or chemotherapy is used; the mortality rate remains high in this age group [51]. Surgical decompression was performed historically but had an increased risk of infection.

13.2 Intermediate-Risk Neuroblastoma

Mild- to moderate-dose chemotherapy is used for intermediate-risk disease, comprising carboplatin, etoposide, cyclophosphamide and doxorubicin, followed by surgery [52]. The number of cycles can be tailored based on the favorable and unfavorable features. The extent of resection has no impact on overall survival, as seen in both CCG and SIOPEN studies, including the experience in our institute [45, 53, 54]. In COG A3961, the favorable and unfavorable groups received chemotherapy comprising 4 and 8 cycles, respectively, and the 3-year EFS and OS were 88% and 96%, respectively. Radiation may be needed for progressive disease or unresectable disease during or after Treatment with chemotherapy [39, 52].

13.3 High-Risk Neuroblastoma

The Treatment of high-risk neuroblastoma generally has three phases: induction therapy, consolidation therapy and maintenance therapy [39]. The induction phase includes chemotherapy and surgical excision. The induction starts with multiple cycles of dose-intensive chemotherapy, including a platinum drug, anthracycline and alkylating agents. Response to therapy at the end of induction chemotherapy is followed by removal of the primary tumor. At the same time, progressive disease is either considered for other chemotherapy (irinotecan/topotecan, temozolomide) and reassessment or best supportive care. The advantage of a gross-total resection over incomplete resection is debatable; however, a safe, complete excision is usually the goal of surgery [55–57]. The consolidation phase involves myeloablative chemotherapy with ASCT (harvested during induction chemotherapy) to repopulate the bone marrow [58–60].

The maintenance therapy is aimed at treating the minimal residual disease after SCT. It includes radiation therapy to the primary site and areas of incompletely resolved metastases, retinoids and anti-GD2 antibody immunotherapy. The retinoids, isotretinoin and the new synthetic retinoid, fenretinide, induce cellular differentiation and slow the growth of neuroblastoma cells. GD2, a disialoganglioside expressed on neuroblastoma cells, is targeted with a chimeric monoclonal antibody known as dinutuximab, along with granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-2 (IL-2) [61–63]. However, significant side effects, including severe pain as GD2, are found on peripheral pain fibers, fever, anaphylaxis with respiratory distress and hypotension. Newer approaches, including difluoromethyl ornithine (DFMO), an ornithine decarboxylase inhibitor, NK cells and CAR-T cells, are being studied katy, [64].

14 Risk-Wise Prognoses with Current Treatment

14.1 Low-Risk Neuroblastoma

Several studies have reported EFS exceeding 90% and OS ranging from 99% to 100% for low-risk diseases [47–49]. The COG-ANBL00P2 study reported 3-year EFS (for a neuroblastoma event) and OS of 97.7% and 100% for expectant observation even without a biopsy in infants under 6 months of age [48]. The COG has now initiated studies (ANBL1232) expanding the criteria for observation without surgery in infants up to 18 months.

14.2 Intermediate-Risk Neuroblastoma

The 3-year OS and EFS rate for intermediate-risk patients was 88% and 95% in the COG A3961 study [52]. In the subsequent COG ANBL0531 study, chemotherapy's duration and intensity were decreased to diminish side effects further. This study had a similar 3-year EFS of 83% and an OS of 95% [65].

14.3 High-Risk Neuroblastoma

The seminal Children's Cancer Group (CCG) phase III cooperative group study with myeloablative chemotherapy with ASCT had a significantly better 3-year EFS (34%) compared to nonmyeloablative chemotherapy (22%) without significant difference in OS (43% vs. 44%) [58]. The benefit in EFS and no change in OS remained on a reanalysis after a longer follow-up [66]. Similar results were observed in a Cochrane review evaluating myeloablative and SCT in a cohort of 739 high-risk patients [67]. The utility of dinutuximab along with GM-CSF and IL-2 in conjunction with isotretinoin over isotretinoin alone was confirmed in a COG phase III trial, which resulted in immunotherapy post-SCT as the standard of care for high-risk disease [61]. The recent randomized COG A3973 study showed better EFS (38%) and OS (50%) were reported compared to the previous studies [68]. The most recent COG-ANBL0532 study had a 3-year EFS of 51.1% and significantly better EFS for tandem transplants (62%) for single SCT (48%) [60].

15 Management of Recurrent Neuroblastoma

Recurrence in patients with high-risk disease carries a dismal prognosis [69]; however, recurrences in patients with low-risk and intermediate-risk neuroblastoma can be salvaged in most patients with observation alone, surgery alone or with moderate-dose chemotherapy, without myeloablative therapy and SCT [47, 52]. Treatment options for recurrent or refractory high-risk patients include chemotherapy (temozolomide, irinotecan/topotecan) combined with immunotherapy.^{131}I-MIBG alone or in combination with other therapy, ALK inhibitors, Crizotinib or lorlatinib for patients with ALK mutations.

16 Summary

- Significant progress has been achieved in the Treatment of patients with neuroblastoma.
- Neuroblastoma is the most common extracranial solid tumor in children.
- Presentation and disease course can be widely variable, ranging from tumors that display spontaneous regression or differentiate into benign variants to those that progress relentlessly despite Treatment and prove fatal.
- More than one-half of patients have widespread metastases at diagnosis.
- Age, stage and amplification of N-myc are important prognostic factors.
- Stratification of patients according to risk guides treatment.
- High-risk, refractory or relapsed tumors remain a clinical challenge.
- Reduction in cytotoxic therapies has been successful in children with low- and intermediate-risk diseases.
- Despite multimodal therapy, the outcomes for patients with high-risk neuroblastoma are suboptimal.
- Continued genomic and biologic characterization advancements will further enhance the identification of tumor-specific targets with therapeutic promise.

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Retinoblastoma

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Abbreviations

AJCC	American Joint Committee on Cancer
COG	Children Oncology Group
EBRT	External beam irradiation
EUA	Examination under anesthesia
IAC	Intra-arterial chemotherapy
IRSS	International Retinoblastoma Staging System
IVC	Intravenous chemotherapy
IViC	Intravitreal chemotherapy
LMIC	Low- and middle-income country
PLONI	Post-laminar optic nerve involvement
RB	Retinoblastoma
SMN	Second malignant neoplasms
TTT	Transpupillary thermotherapy

1 Introduction

Retinoblastoma (RB) is the most common malignant intraocular neoplasm in children [1]. Although long-term survival has improved to well over 90% with multimodality therapy in the developed world, it still causes fatalities in the low- and middle-income countries (LMICs) because of delayed presentation and treatment abandonment [2]. The management of RB has evolved over the past few decades and brought about a paradigm change from enucleation being the primary modality of therapy to a more multimodality treatment with an increased focus on globe preservation. The aim of RB therapy is not only to preserve life and eye but also to optimize residual vision and lately to focus on decreasing second malignancies. Early diagnosis of RB with the disease contained within the eye is key to better survival.

2 Incidence and Epidemiology

Retinoblastoma constitutes 2.5%–4% of all pediatric cancers with 11% occurring in less than 1 year of age [3]. About 8000 children worldwide are diagnosed with RB each year with an estimated incidence in India being 1200 cases annually. The age-adjusted incidence rates of RB in developed countries are 2–5 per million children (approximately 1:15,000 to 1:20,000 live births) [4] where RB is diagnosed early, in the intraocular stage, in 90% of cases with the median age of diagnosis of unilateral and bilateral RB at 24 months and 13 months, respectively [5]. In India, as in many other LMICs, the median age of diagnosis of unilateral and bilateral RB is 30 and 24 months, respectively, and only 60% of RB is diagnosed in the intra-ocular stage, with one-third presenting as locally advanced or metastatic disease [6]. Thus, India has a major burden of RB and the delay in diagnosis attributed to socio-economic barriers, leading to a large proportion of advanced disease presentations, which result in poorer outcomes [7–9].

3 Biology of Retinoblastoma

Retinoblastoma is the first tumor where a genetic origin was identified [10]. Knudson proposed the "two-hit hypothesis" in 1971, though the Rb1 gene was discovered later in 1986. According to Knudson's two-hit hypothesis, mutation in the 2 alleles of Rb1 gene results in the development of RB in children [11]. The Rb1 gene on chromosome 13q14.2 is composed of 27 exons that encode for 110kD nuclear phosphoprotein (pRb) [12]. Rb1, a tumor suppressor gene, is a regulator at the cell cycle checkpoint between G1 and entry into S phase [13]. In the heritable form, the first hit on the Rb1 allele occurs in the germ cell (germline mutation),

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which affects every cell in the body, and the second hit occurs in the Rb1 allele of the retinal precursor cell during retinal development (somatic mutation). The hereditary RB also predisposes patients to second cancers like osteosarcoma, soft tissue sarcoma, and pineoblastoma (trilateral RB) [14]. The germline mutation of the Rb1 gene in the heritable RB is inherited from a carrier in 25% cases and the rest of 75% cases it occurs as a "de novo" mutation early in embryogenesis. In the "sporadic" nonheritable form, the two hits occur in the retinal precursor cell (somatic mutations) and the mutation is confined only to the retinal cells [15]. Additional genetic events predisposing to RB transformation include P53 pathway alterations like MDM2, MDM4 amplification, and epigenetic changes due to BCOR mutations and SYK upregulation [16, 17]. Rb1 gene mutations have been associated with >95% of RBs; however, there is a small subgroup of patients (2.7%) with RB with wild-type Rb1 and who were found to have MYCN amplification [18].

Retinoblastoma arises from the sensory retina and grows initially into the intraocular compartments like choroid, vitreous, and anterior chamber. There are two growth patterns of RB, exophytic (away from vitreous) and endophytic (towards vitreous). Exophytic RB arising from outer layers of retina results in subretinal seeds and retinal detachment. Endophytic RB arising from the inner retinal layers causes vitreous seeding. Other types of growth patterns include mixed (both endophytic and exophytic growth) and diffuse infiltrating orbital pattern. Patients with tumor extending into the anterior chamber can present with white fluffy exudates in the anterior chamber [19]. As there is a delay in diagnosis, it spreads to extraocular compartments involving the orbit, optic nerve, and distant metastatic sites.

4 Clinical Presentation

Two-thirds of the retinoblastoma cases are diagnosed before 2 years of age and 95% of cases diagnosed before 5 years of age [3]. There are two distinct patterns of clinical presentation. The majority of patients (60%) have sporadic, nonhereditary RB presenting with unilateral or unifocal disease and present at the median age of 30 months.The hereditary RB resulting in bilateral or multifocal disease occurs in 40% of patients [20] and presents earlier at a median age of 14–16 months.

Retinoblastoma patients with early intraocular disease present commonly with leucocoria (white eye reflex) in 70% followed by strabismus (15%) and nystagmus (10%). Leucocoria when clinically detectable without an ophthalmoscope indicates advanced intraocular disease occupying atleast 50% of retina (Fig. 1a). Strabismus occurs when RB involves macular region of the retina. Patients with advanced intraocular RB can present with rubeosis iridis, hyphema, hypopyon, and glaucoma. Retinoblastoma diagnosis should always be looked for in a child presenting with spontaneous hyphema in the absence of trauma or who presents with signs of endophthalmitis. Pain is uncommon in intraocular RB unless secondary glaucoma or inflammation is present. Extraocular RB presenting with proptosis (Fig. 1b), preauricular lymphadenopathy, bone pains, or central nervous system symptoms (headache, vomiting, seizures, etc.) is rare in developed countries [6]. However, one-third of RB in LMICs present with orbital disease or metastases and is the major cause of mortality, with the reported incidence ranging between 9% and 11% [21, 22].

Retinoma (or retinocytoma) is a spontaneously arrested/regressive form that resembles treated RB and on ophthalmoscopy appears as gray lesion with intense calcification and a zone of atrophy around the lesion. Retinocytoma can be detected in a parent of a child with RB. These lesions must be carefully monitored in young children, as they can occasionally progress to active RB [23, 24]. Differential diagnoses such as Coats disease, persistent hyperplastic primary vitreous, medulloepithelioma, uveal melanoma in children, retinal detachment due to other causes, *Toxocara canis* infection, etc. should be ruled out while evaluating a suspected RB [25].

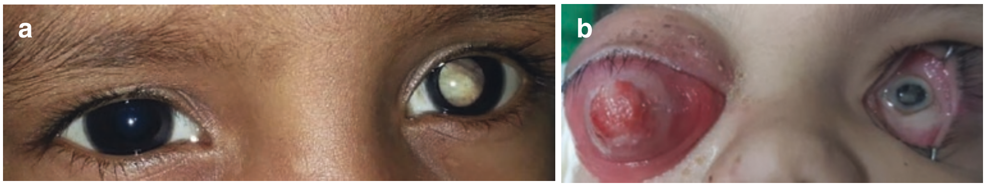

Fig. 1 Clinical manifestations of retinoblastoma (**a**) leucocoria in a case of left eye retinoblastoma (intraocular). (**b**) Advanced bilateral retinoblastoma; proptosis due to orbital (extraocular) retinoblastoma (right eye) and left eye pthisis bulbi

5 Evaluation and Workup

Retinoblastoma is a clinico-radiological diagnosis and biopsy is usually not required.

5.1 Examination Under Anesthesia (EUA)

Any child with suspected RB should undergo EUA for direct visualization of the tumor by the ophthalmologist who has the requisite experience in RB. Retinoblastoma appears as a mass projecting into the vitreous, but presence of retinal/vitreal hemorrhage or a corneal/lenticular opacity may make its visualization difficult. During EUA, the ophthalmologist should look for laterality (unilateral or bilateral), location of tumors (posterior/anterior), tumor size (diameter, thickness) and number, subretinal fluid and tumor seeds, vitreous seeds, iris neovascularisation, hyphema, hypopyon, and anatomic relationship of tumor to optic disc and macula. Additionally, evaluation of corneal diameters and intraocular pressure measurement should be done during the EUA session. A wide-angle retinal imaging systems such as RetCam provide a 130-degree field of view and digital recording and helps in diagnosis and monitoring (Fig. 2).

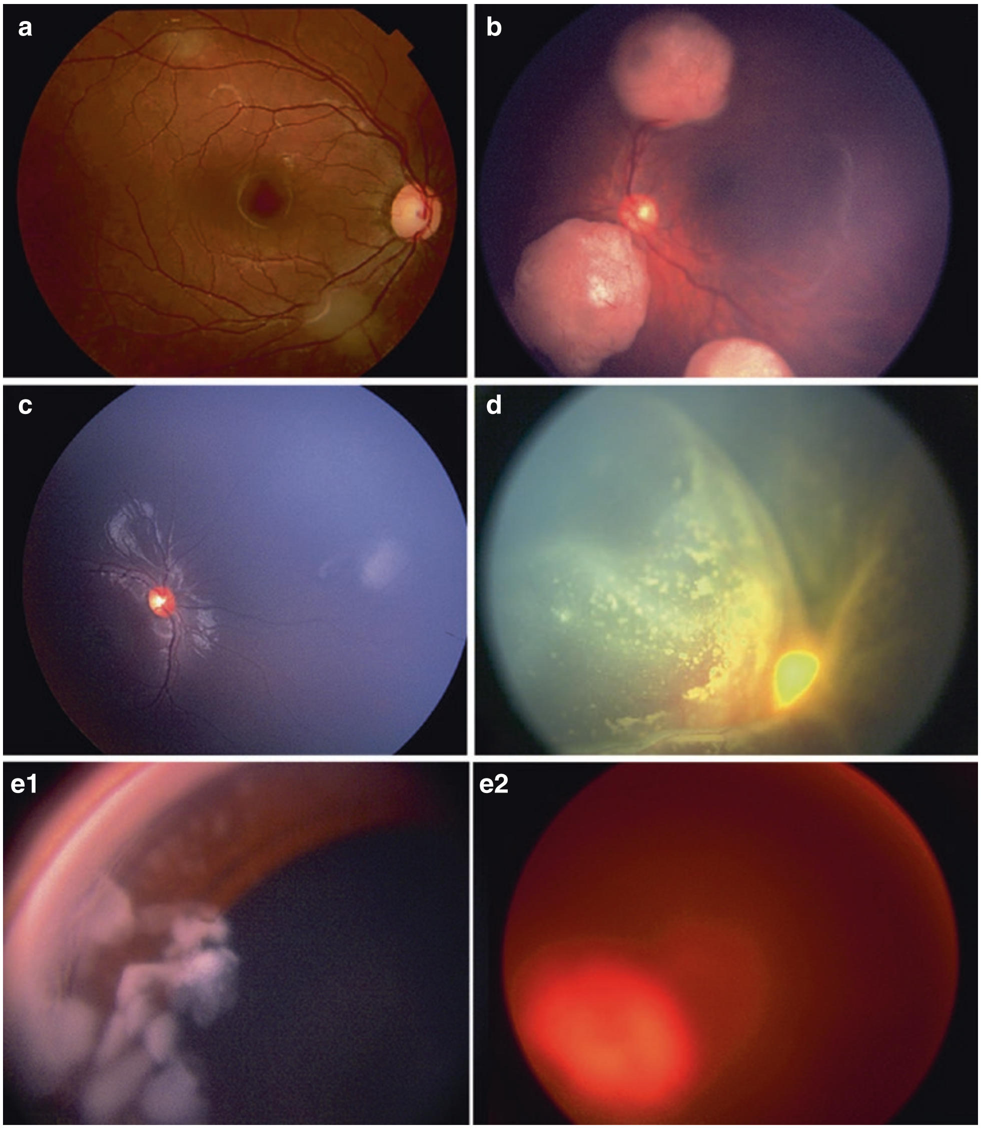

Fig. 2 RetCam imaging showing (**a**) intraocular ICRB Group A retinoblastoma, (**b**) Group B retinoblastoma—multiple endophytic tumors, (**c**) Group C retinoblastoma (**d**), Group D retinoblastoma with diffuse subretinal seeds, (**e1**) Group E retinoblastoma with anterior segment invasion, (**e2**) Group E retinoblastoma—large tumor with intraocular hemorrage

5.2 Ultrasonography (B-Scan)

Ultrasonography detects intra-tumoral calcification in 92%–95% of cases. The presence of calcification (Fig. 3) is key to diagnosis (present in 95% of RB) [26]. In case of RB, it can detect laterality, number, size and location of tumors, and RB-related complications like retinal detachment and vitreal hemorrhage. It also helps to rule out other causes of leucocoria like PHPV, Coats disease, retinopathy of prematurity, toxocariasis, and other infections.

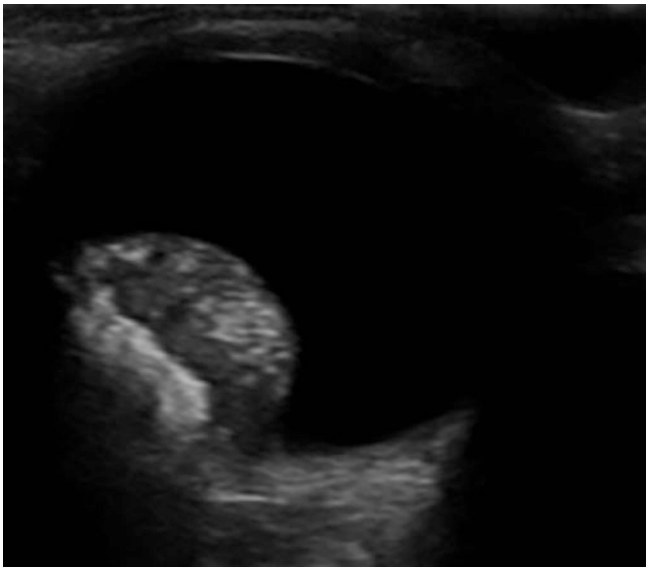

Fig. 3 Ultrasound showing intraocular mass with calcifications

5.3 MRI with Contrast

MRI of both orbits and brain with contrast is the imaging modality of choice for local staging. MRI gives an adequate resolution for the diagnosis of extraocular soft tissue disease (Fig. 4). Optic nerve involvement is indicated by abnormal contrast enhancement of the nerve, optic nerve thickening, and/or interruption of the normal linear enhancement at the optic nerve disc. Although MRI is an excellent modality for accurately assessing the extraocular extent of RB, EUA remains the optimal modality for assessing the intraocular component. However, MRI aids in detecting scleral and choroidal infiltration and pattern of tumor growth. Additionally, MRI brain is useful in detecting trilateral RB (pineoblastoma or suprasellar mass) and leptomeningeal disease. It is also a useful modality in differentiating RB from Coats disease and persistent hyperplastic primary vitreous [27].

CT scan is used occasionally in difficult cases to look for calcifications or else is only indicated if an MRI scan is not available.

5.4 Bone Marrow Studies and CSF Examination

Distant metastatic workup including bilateral bone marrow aspiration with biopsy and CSF studies should be considered in cases of advanced disease with evidence of extraocular RB at presentation or involvement of the optic nerve. Bone scan is rarely indicated in symptomatic patients only [28].

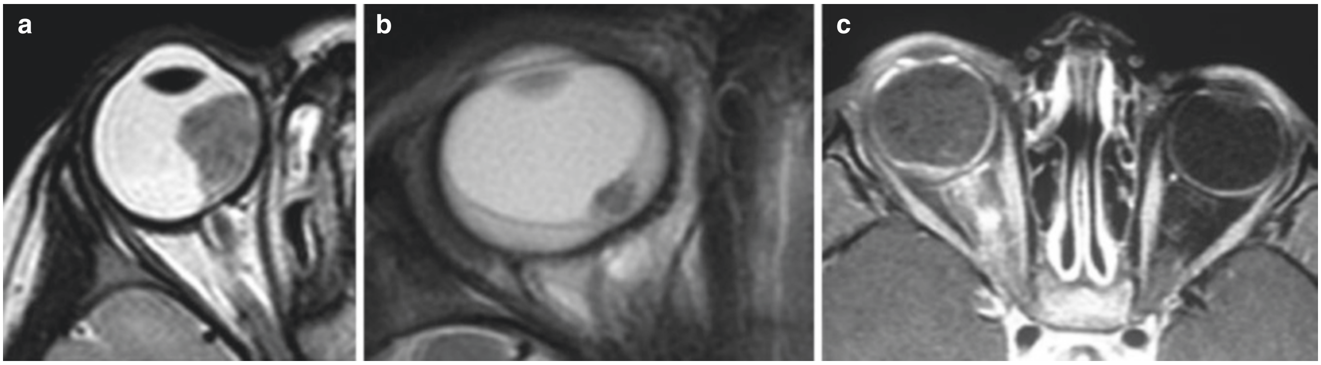

Fig. 4 MRI of orbit showing intraocular mass with endophytic (**a**), exophytic growth (**b**), and optic nerve (**c**) involvement

6 Grouping and Staging of Retinoblastoma

Risk stratification of RB includes two components: tumor grouping and staging.

Grouping System: For assessment of intraocular tumors and prognosticates globe and vision salvage

(a) Reese–Ellsworth Classification for Intraocular Tumors

This classification was introduced to prognosticate patients treated with methods other than enucleation. It predicts eye salvage with external beam irradiation [29]. The classification was devised before the widespread use of indirect ophthalmoscopy and evolution of focal treatments.

(b) International Classification of Retinoblastoma (ICRB, 2003) (Table 1)

This new classification is based on the extent of tumor seeding within the vitreous cavity and subretinal space, along with tumor size and location. This classification prognosticates vision. It also helps in predicting high-risk pathology [30].

Staging System: Prognosticates survival in RB.

(a) International Retinoblastoma Staging System (IRSS) (Table 2)

International Retinoblastoma Staging System (IRSS) has been proposed by an international consortium of ophthalmologists and pediatric oncologists (see Table 2). It is the more widely used RB staging system in the clinical setting [29, 31].

(b) American Joint Committee on Cancer (AJCC) staging system can be found in AJCC Cancer Staging Manual, Eighth Edition, Page no. 825–826, Chapter no. 68, Retinobhlastoma, Table: Definition of TNM which can be accessed at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5998398/The eighth edition of AJCC cancer staging system for Retinoblastoma includes a hereditary (H) component, making it the cTNMH scheme (c for clinical). The cTNMH categories are based on whether the retinoblastoma is determined to be intraretinal, intraocular, advanced intraocular or extraocular. The TNM scheme also has a pathological (pTNM) sub-classification that is widely used by ophthalmic pathologists [32]. AJCC RB classification is a comprehensive staging that incorporates intraocular and extraocular RB, with the power to predict both globe and life salvage especially in patients from developing countries where the majority present with advanced stage disease [33].

Table 1 International Classification of Retinoblastoma (ICRB)

Group	Definition
Group A	• Small intraretinal tumors away from foveola and disc All tumors that are 3 mm or smaller in greatest dimension, confined to the retina andall tumors are located further than 3 mm from the foveola and 1.5 mm from the optic disc
Group B	• All remaining discrete tumors confined to the retina All other tumors confined to the retina not in Group A Tumor-associated subretinal fluid less than 3 mm from the tumor with no subretinal seeding
Group C	• Discrete local disease with minimal subretinal or vitreous seeding Tumor(s) are discrete Subretinal fluid, present or past, without seeding involving up to one-fourth of the retina Local fine vitreous seeding may be present close to discrete tumor Local subretinal seeding less than 3 mm (2 DD) from the tumor
Group D	• Diffuse disease with significant vitreous or subretinal seeding Tumor(s) may be massive or diffuse Subretinal fluid present or past without seeding, involving up to total retinal detachment Diffuse or massive vitreous disease may include "greasy" seeds or avascular tumor masses Diffuse subretinal seeding may include subretinal plaques or tumor nodules
Group E	• Presence of any one or more of the following poor prognosis features: Tumor touching the lens Tumor anterior to anterior vitreous face involving ciliary body or anterior segment Diffuse infiltrating retinoblastoma Neovascular glaucoma Opaque media from hemorrhage Tumor necrosis with aseptic orbital cellulitis Phthisis bulbi

Table 2 International retinoblastoma staging system

IRSS Stage	Definition
0	Eye with no dissemination of disease and managed conservatively (refer to RB grouping)
I	Eye enucleated, completely resected histologically
II	Eye enucleated but with microscopic residual disease • Trans-scleral invasion • Positive cut end of optic nerve
III	Regional extension • Overt orbital disease • Pre-auricular or cervical nodal involvement
IV	Metastatic disease • Haematogenous metastasis • CNS extension – Pre-chiasmatic involvement – CNS mass – Leptomeningeal and CSF disease

7 Prognostic Factors

In unilateral RB, the prognosis for vision is very good for the unaffected eye, as the development of tumors in the unaffected eye is rare after 3 years of age. In bilateral RB, prognosis of vision depends on the extent of the tumor involvement and effectiveness of treatment modalities. The prognosis of vision in the involved eye is good if the tumors are small and away from the fovea. In cases of intraocular RB, the chances of ocular salvage decrease with more advanced disease, as in Groups D and E. In case of extraocular RB, survival is the goal of treatment and all patients will undergo enucleation of the involved eye with the addition of external beam RT and chemotherapy. The metastatic disease which occurs in~10% of RB patients from LMICs is associated with poor prognosis, especially CNS metastases [34].

7.1 Histopathologic Risk Factors

Histopathologic risk factors help in predicting the occurrence of metastasis in children with RB. Most important histopathologic prognostic indicators for development of metastasis include post-laminar optic nerve involvement at the site of surgical transection of the nerve and extrascleral extension of tumor into the orbit. As children in a developing country have delay in diagnosis, 54% of them present with such high-risk features compared to 20% of children in developed countries. Other high-risk histolo-pathologic features include massive choroidal invasion of ≥3 mm, post-laminar optic nerve involvement (PLONI) without cut end positivity [35, 36].

Escalation of treatment with adjuvant chemotherapy in the presence of these high-risk histopathologic features has shown to reduce the incidence of metastasis to 4%, compared to 24% who did not receive adjuvant therapy [37]. Also, a recent prospective study on high-risk histopathologic features in unilateral RB by COG found 3 mm or greater choroidal invasion in the peripapillary posterior choroid (around the head of the optic nerve) in combination with PLONI (≥1.5 mm) confer a poorer prognosis and lumbar puncture is recommended in such patients and if CSF negative for malignancy, orbital irradiation to be considered [38].

8 Genetic Testing and Genetic Counseling

Retinoblastoma is inherited in an autosomal dominant pattern with almost complete penetrance (85%–95%) [39]. Mutation in the Rb1 gene, located at 13q14.2, leads to loss of function that inactivates the Rb1 protein. In hereditary RB, germline mutation ("first hit") occurs mainly due to submicroscopic point mutations (75%–80% of cases) and large deletions involving the Rb1 gene, which can be detected by conventional cytogenetics is rare (3%–5%) [10]. Such large deletions involving 13q also lead to mental retardation, dysmorphism, and RB (13qdeletion syndrome) [40]. Somatic mutations (second hit) occur spontaneously at a rate of 1:1000. The majority of these mutations are chromosomal (50% mitotic recombination, 40% non-disjunction, and 10% deletions) [41]. These somatic mutations are more sensitive to radiation.

Genetic testing and counseling are indicated in all patients with RB and their families. Mutations are distributed throughout the 27 exons of the Rb1 gene. Suspected "hotspots" account for only 40% of these mutations. The rest of the mutations are scattered throughout the entire gene, most frequently in exons 9, 10, 14, 17, 18, 20, and 23 [42]. A single genetic test is unlikely to detect all germline RB gene mutation. Currently, it is necessary to combine various modalities such as DNA sequencing, FISH, MLPA, PCR, Methylation studies to increase the sensitivity of detection of Rb1 gene mutation to 90%–95%. Testing of the germline RB1 mutation is done on peripheral blood or saliva.

In patient with unilateral disease, tumor DNA can be used for detecting the two Rb1 gene mutations. The mutations identified in the tumor DNA can be sought in leucocyte DNA of peripheral blood or saliva of the patient. If one of the mutations is detected in the leucocyte DNA then it is a heritable form of RB. If neither of the mutation is identified in leucocyte DNA, then chances of it being heritable RB, cannot be conclusively ruled out due to the occurrence of low-level mosaicism. In such a scenario, proband's offsprings need to be tested for RB gene mutations detected in the tumor DNA, and genetic testing is not required in other family members. If tumor sample is unavailable and leukocyte DNA did not reveal a mutation, the chance for an undetected germline mutation is approximately 1% to 1.5%. In such a scenario, screening of the unaffected eye should occur until age 5. The offspring of such children should also undergo surveillance.

In bilateral disease, germline mutation can be identified in the leucocyte DNA in the peripheral blood/saliva in 95% of children. If the mutation cannot be identified in peripheral blood in a patient with bilateral disease and tumor DNA shows both mutations, low-level mosaicism is assumed and the proband's offspring is at risk of RB and needs surveillance [10]. If germline mutation is not identified by conventional methods and the patient has a positive family history, then linkage analysis can be used to clarify the mutation status of at-risk family members [43].

All future children of a proband with heritable RB have a 45% chance of developing RB (Table 3). Risks of RB for the siblings of the proband depend on parental status. If a parent has a history of RB, retinoma, or positive genetic testing

Table 3 Risk of developing retinoblastoma in siblings and offspring of patients

Subjects	Probability of disease (%)
Subjects with carriers of RB1 gene mutation	90
Offspring of patient with bilateral retinoblastoma	45
Sibling of patient (if either parent is affected)	45
Sibling of patient with bilateral disease (with parents unaffected)	2
Sibling of patient with unilateral disease (with parents unaffected)	1

results, future offsprings have a 45% risk of RB. If neither parent's testing reveals the familial RB1 mutation, subsequent children have a 2% to 3% chance of inheriting the mutation due to undetectable low-level mosaicism in one of the parents [39]. Any unaffected child with germline RB1 mutation should be examined every 3–4 weeks under anesthesia until the age of 1 and then every 3–4 months until the age of 5 years.

9 Principles of Management

Priorities in management of RB include cure, eye salvage, and vision preservation followed by prevention or early detection of second malignant neoplasms. Retinoblastoma management is a multidisciplinary approach including pediatric oncologist, ocular oncologist (ophthalmologist), radiation oncologist, genetic counselor, radiologist, pathologist, and other support staff. Retinoblastoma management must be individualized based on stage, group, and presence of bilateral disease. Major concepts in management include decisions regarding ocular preservation versus enucleation, avoiding or delaying radiation for ocular salvage, and risk-adapted therapies in extraocular versus intraocular RB.

9.1 Treatment Options

Treatment options include surgery (enucleation and orbital exenteration), focal therapies (laser photocoagulation, cryotherapy, thermotherapy, chemothermotherapy, and plaque radiotherapy), chemotherapy (intravenous, subconjunctival, intravitreal, and intra-arterial), and radiation (external beam irradiation and proton therapy).

9.1.1 Enucleation

Enucleation is the treatment of choice for advanced RB with tumor invading the optic nerve, orbit, and when there is no hope for salvage of useful vision in the affected eye. Enucleation involves gentle removal of the intact eye without seeding the malignancy into the orbit. Special care should be taken to perform all steps in a controlled fashion to avoid globe perforation or compression. For optimal staging, 10–15 mm long section of the optic nerve needs to be removed with the globe. During the same procedure an orbital implant is usually fitted, and the extraocular muscles are attached to it. Different orbital implants include polymethylmethacrylate, polyethylene, and coralline and bovine hydroxyapatite spheres. Implant motility with little resistance in the orbit is usually achieved by attaching the four rectus muscles anatomically to a tissue wrap placed around the implant. Judicious use of chemotherapy, surgery, and radiation therapy in patients with orbital disease usually results in effective tumor control, avoiding the need for orbital exenteration.

9.1.2 Focal Therapies

Laser Photocoagulation

Laser photocoagulation is used to treat small posterior RB of size ≤4.5 mm in diameter and ≤2.5 mm thickness with no evidence of vitreous seeds. Under indirect ophthalmoscopy, argon or diode laser is used to produce overlapping spots at the edge of the tumor in order to coagulate all the blood supply to the tumor [44]. Two to three sessions at 1-month interval are adequate to control 70% of properly selected tumors. Recurrences are treated with plaque radiotherapy [45]. Complications include serous retinal detachment, retinal vascular occlusion, retinal traction, retinal hole, and preretinal fibrosis.

Cryotherapy

Cryotherapy is used to treat peripheral small RB of size ≤3.5 mm in diameter and ≤2.5 mm thickness with or without overlying focal vitreal seeds. Cryotherapy causes cell lysis by disruption of the cell membrane that occurs after the formation of cytoplasmic ice crystals. Under direct visualization, nitrous oxide gas is used to deliver the trans-scleral freeze using a cryoprobe. One or two sessions of triple freeze–thaw cryotherapy at 1-month interval help in achieving tumor control [46]. Complications include serous retinal detachment, retinal tear, localized preretinal fibrosis, and rhegmatogenous retinal detachment.

Transpupillary Thermotherapy (TTT)

In transpupillary thermotherapy, ultrasound, microwaves, or infrared radiation delivers hyperthermia (45–65 °C) at subphotocoagulation temperatures, which results in tumor cytotoxicity. Under indirect ophthalmoscopy, semiconductor diode laser is used to deliver large spots (2–3 mm) with prolonged burn duration. The desired endpoint is a subtle whitening of the tumor free of hemorrhage. Complete tumor regression can be achieved in over 85% of tumors using three to four sessions of thermotherapy [45]. Thermochemotherapy is becoming a very important component in the treatment of intraocular RB where sequential administration of thermotherapy with carboplatin enhances the antitumor effect by increasing the platinum-DNA adducts [47]. Complications include focal iris atrophy, focal paraxial lens opacity, retinal scarring, retinal traction, and serous retinal detachment.

Plaque Radiotherapy

Plaque radiotherapy is a form of brachytherapy used to treat solitary RB with 6–15 mm diameter, ≤8 mm thickness, and lesion more than 3 mm away from the optic disc or fovea. The radioisotopes are loaded on an applicator (gold or silver) and the plaque sutured onto the episclera. The total dose of 40Gy is delivered over a period of 2–5 days. Commonly used radioisotopes include Iodine-125, Iridium-192 (emits gamma rays), and Ruthenium-106 (emits beta rays). In majority of cases (70%), it is used as secondary treatment after failure prior therapy [48]. Tumor control and globe salvage can be achieved in nearly 90% of cases. Positive visual outcomes have been reported in 62% of cases [49]. Plaque radiotherapy with focal, shielded radiation fields, has least chance of inducing second malignant neoplasm. Complications include radiation retinopathy and papillopathy especially in patients receiving systemic chemotherapy.

9.1.3 Systemic Chemotherapy

Successful management of RB using chemotherapy along with local surgical methods can reduce the need for external beam irradiation and therefore reduce the risk of second malignancies, orbital and facial growth abnormality due to radiation [50]. Systemic or intravenous chemotherapy can be administered in following three clinical settings.

Chemoreduction

The main objective of chemotherapy in localized intraocular RB has been to reduce the size of the tumors (chemoreduction) to an extent that would allow use of focal therapies and can eliminate the use of external beam irradiation and avoid enucleation. The commonly used chemotherapy regimen in intraocular RB contains vincristine, carboplatin, and etoposide (VEC regimen). Other chemotherapy agents which are active in RB include cyclophosphamide, doxorubicin, and cisplatin. Usually two to four chemotherapy cycles are used. Chemoreduction can be used in unilateral and bilateral RB and in all stages of disease, but advanced intraocular disease (GroupD/E) shows highest failure rate. Shields et.al showed chemoreduction success correlated with ICRB grouping with Groups A, B, and C attained over 90% control, whereas Group D showed only 47% control, and Group E was mostly enucleated [29]. There is increased risk of recurrence of retinal tumor and vitreal seeds in eyes with subretinal seeds at initial evaluation. These recurrences occur typically in the first 3 years [51]. In addition, at 5 years follow-up, 24% of patients develop new RB at a mean interval of 5 months, most commonly in patients with disease onset at infancy and family history of RB [52]. Careful follow-up of patients treated with chemoreduction is important.

Chemoprophylaxis

Chemoprophylaxis is given in patients with post enucleated specimens with high-risk histopathological features. The high-risk histopathological features may be associated with a higher risk of systemic metastasis and/or local recurrence and thus aim of chemotherapy is to reduce local/systemic relapse [37]. These high-risk histopathologic features include invasion of anterior chamber, iris invasion/ ciliary body invasion, transcleral invasion / extra scleral disease, and optic nerve resection margin positive [53]. However, observation for isolated massive choroidal invasion may be considered in centers where pathological expertise is available and the possible relapse could be salvaged. In centers where the facilities are not available, massive choroidal invasion must be considered as an indication for chemoprophylaxis. At least six cycles of chemotherapy is used in the presence of such high-risk pathologic features [54].

Chemoprevention

In patients in gross/microscopic residual extra-ocular disease, 6–12 cycles of chemotherapy is given along with external beam irradiation. Aim of chemoprevention is to rapidly reduce the tumor bulk and control the micrometastatic disease.

9.1.4 Local Delivery of Chemotherapy

Intra-arterial Chemotherapy (IAC)

IAC is a method of local delivery of chemotherapy for RB that results in high intraocular concentration of the drug without associated systemic adverse effects [55]. Through trans-femoral approach, the ostium of the ophthalmic artery is superselectively catheterized, and the bolus of chemotherapy is infused through the femoral catheter. Melphalan (3–7.5 mg), carboplatin (15–50 mg), and topotecan (1–2 mg) are the commonly used agents. IAC can be a one-, two-, or three-drug regimen based on the intraocular stage of the tumor. It is repeated every 4 weeks, and most of the patients require three sessions to achieve an adequate tumor response. The ocular salvage rate is around 90% for untreated eyes and around 60% for eyes that failed prior therapies [56]. Various studies comparing IAC with intravenous chemotherapy (IVC) suggest IAC leads to shorter time to success, lower number of relapses, improved ocular survival, and visual outcome [57]. However, the use of this technique requires unique resources including an interventional radiologist, pediatric anesthetic services, and an experienced ocular oncologist. Complications associated with IAC include vitreous hemorrhage, retinal artery obstruction, ophthalmic artery spasm with reperfusion, partial choroidal ischemia, optic neuropathy, etc.

Intravitreal Chemotherapy (IViC)

Vitreous seeds are aggregates of tumor cells found in the avascular vitreous. Vitreous seeds are relatively resistant to the effect of intravenous chemotherapy due to lack of blood supply. Refractory vitreous seeds are either persistent (does not disappear with chemoreduction) or recurrent (disappears during chemoreduction and recurs) [58]. Despite intra-arterial chemotherapy, vitreal seeds remain the main cause of secondary enucleation and indication for external beam irradiation. With intravitreal chemotherapy, higher drug concentration can be achieved within the vitreous, and it effectively causes regression of vitreous seeds, without associated systemic side effects. Melphalan (20–30 μg) and topotecan (20–30 μg) are the commonly used agents in IViC. After injecting the drug, the application of triple freeze–thaw cryotherapy at the injection site prevents the egress of the tumor cells in the needle track [59]. With melphalan, vitreous seed regression ranging from 85% to 100% of eyes and globe salvage in 80%–100% of eyes have been reported. By combining intra-arterial and intra-vitreal chemotherapy in advanced intraocular disease, it is possible to reduce the treatment duration, cost, and reduce the need for enucleation and external beam irradiation.

Intracameral Chemotherapy (ICC)

ICC is a novel conservative method of delivering chemotherapy directly into the anterior chamber in selected cases of eyes with secondary anterior chamber seeding, with encouraging results. However, longer follow-up is needed to assess safety and efficacy [60].

9.1.5 External Beam Irradiation (EBRT)

Retinoblastoma is a highly radiosensitive tumor. With the advent of chemotherapy, the role of radiotherapy is very limited in the primary management of RB. External beam irradiation induces second cancers in the field of irradiation. In cases of bilateral RB, the cumulative incidence of second cancers at 50 years is reported to be 51% based on a very large series from New York [61]. It can also lead onto orbital hypoplasia, cataract, and dry eye syndrome.

Currently, EBRT is used in patients presenting with advanced RB such as overt orbital disease and intraocular RB not responding well to conservative management, especially with diffuse vitreal and/or subretinal seeds, when globe salvage is the priority and after enucleation with high-risk features (transscleral involvement and an optic nerve cut end involvement). The ideal dose is 40–45 Gy given in fractionated doses of 180–200 cGy over 3–4 weeks with lens-sparing technique with photon beam delivered using linear accelerator [62]. Proton therapy is a recent modality of EBRT with early reports showing encouraging results [63]. Sethi et al. in their retrospective series showed, in patients who received proton therapy there was 0% 10-year cumulative incidence of second malignant neoplasm in the RT field compared to 14% in photon therapy. Overall second malignant cancers were 5% in proton therapy arm compared to 14% in photon therapy [64].

10 Tata Memorial Hospital Management Algorithms for Retinoblastoma (Figs. 5 and 6)

10.1 Treatment of Extraocular Retinoblastoma

10.1.1 Orbital Retinoblastoma

For patients with macroscopic orbital disease, two to four cycles of chemotherapy are administered upfront followed by enucleation. Additional cycles of adjuvant chemotherapy (total of 12 cycles) are administered [65]. Adjuvant orbital irradiation (40–45 Gy) is required to consolidate local control. If there is a recurrence after the above treatment, orbital exenteration should be considered. Patients with isolated involvement of optic nerve at the transection level require a similar treatment approach and irradiation should include entire orbit (36 Gy) with 10 Gy boost to the optic chiasm. In cases of pre-auricular and/or cervical nodal involvement irradiation to the involved nodes should be carried out. Patients with accidental ocular perforation or intraocular surgery for unsuspected RB should be managed in line with orbital RB.

10.1.2 Retinoblastoma with Systemic Metastasis

Patients with involvement of central nervous system (including trilateral RB) have a very poor outcome and most succumb to their disease despite intensive systemic chemotherapy and intrathecal chemotherapy. Therapy intensification with high-dose chemotherapy with autologous stem cell rescue also has not shown to improve outcomes. However, in metastatic RB not involving CNS (isolated hematogenous metastasis), high-dose chemotherapy with carboplatin, etoposide, and thiotepa followed by autologous SCT has shown to improve outcome in a recent Children Oncology Group (COG) prospective study with 3-year EFS of 79% [66].

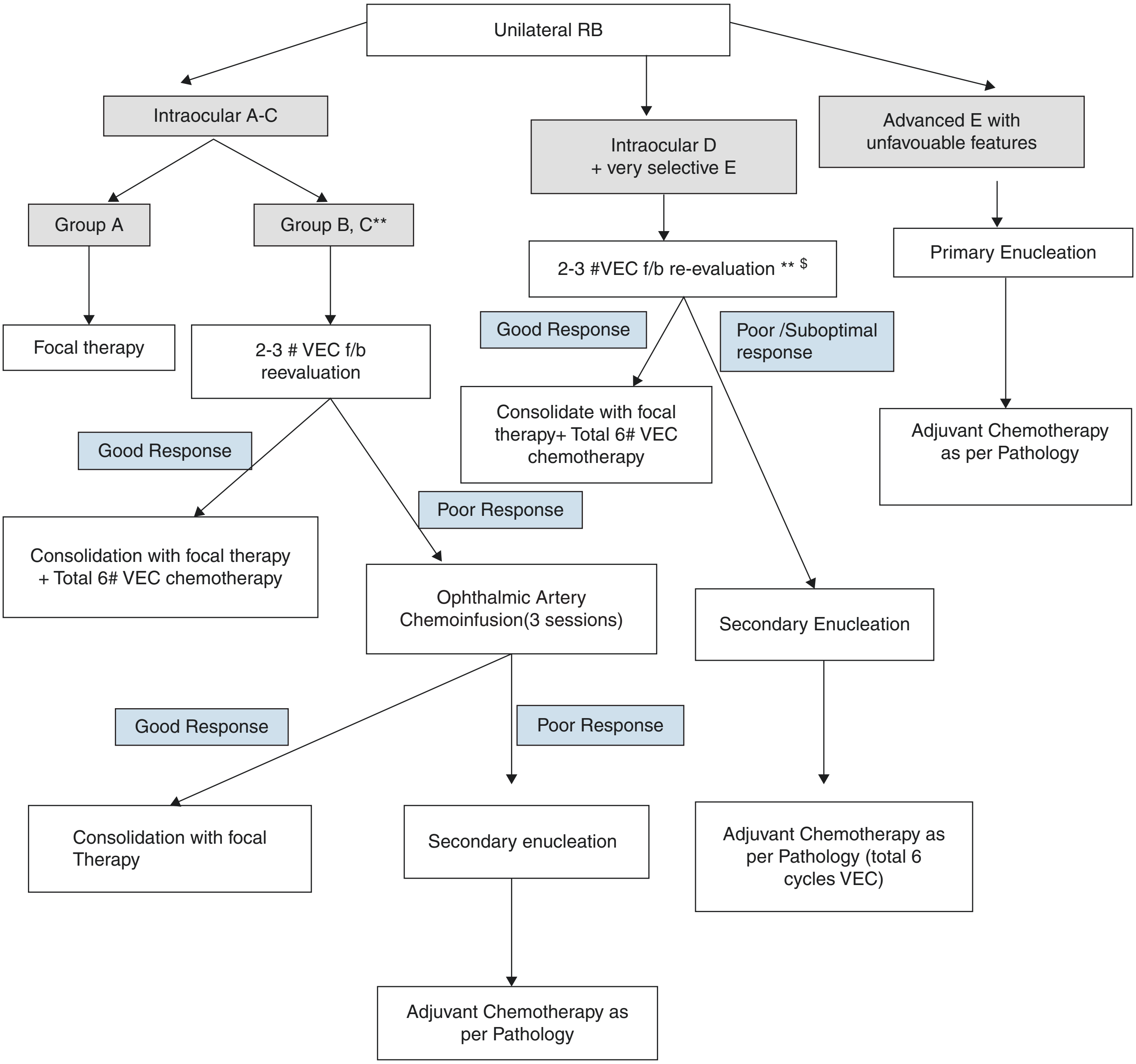
Unilateral RB
Intraocular A-C
Intraocular D
+ very selective E
Advanced E with
unfavouable features
Group A
Group B, C**
2-3 #VEC f/b re-evaluation ** $
Primary Enucleation
Focal therapy
2-3 # VEC f/b
reevaluation
Good Response
Poor /Suboptimal
response
Consolidate with focal
therapy+ Total 6# VEC
chemotherapy
Adjuvant Chemotherapy
as per Pathology
Good Response
Poor Response
Consolidation with focal therapy
+ Total 6# VEC chemotherapy
Ophthalmic Artery
Chemoinfusion(3 sessions)
Secondary Enucleation
Good Response
Poor Response
Consolidation with focal
Therapy
Secondary enucleation
Adjuvant Chemotherapy as
per Pathology (total 6
cycles VEC)
Adjuvant Chemotherapy as
per Pathology

Fig. 5 Treatment of unilateral retinoblastoma algorithm

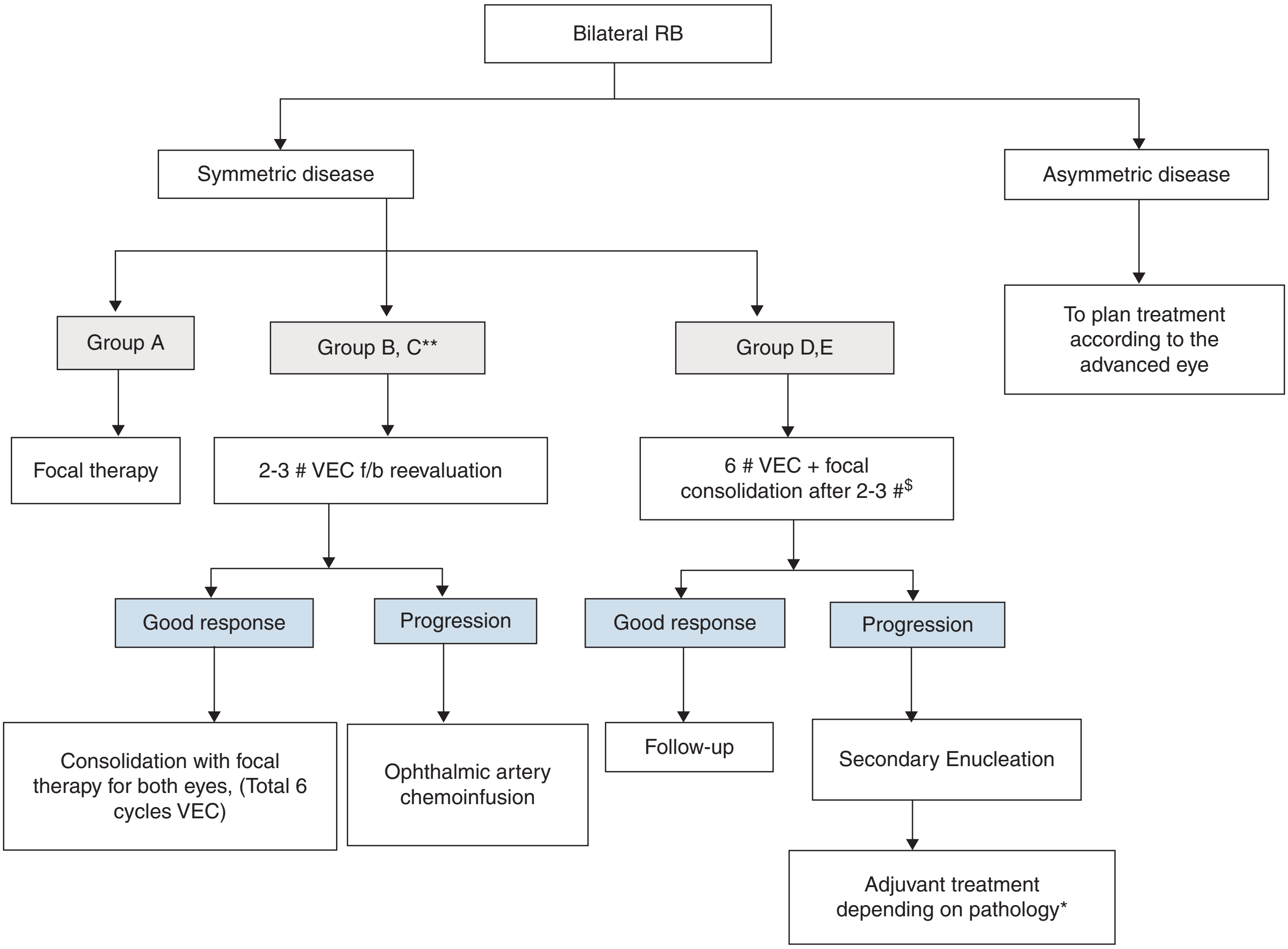
Bilateral RB
Symmetric disease
Asymmetric disease
Group A
Group B, C**
Group D,E
To plan treatment according to the advanced eye
Focal therapy
2-3 # VEC f/b reevaluation
6 # VEC + focal consolidation after 2-3 #$
Good response
Progression
Good response
Progression
Consolidation with focal therapy for both eyes, (Total 6 cycles VEC)
Ophthalmic artery chemoinfusion
Follow-up
Secondary Enucleation
Adjuvant treatment depending on pathology*

Fig. 6 Treatment of bilateral retinoblastoma

11 Long-Term Effects of Retinoblastoma Therapy

11.1 Second Malignant Neoplasms (SMN)

Cumulative incidence of SMN in patients with germline mutations of the Rb1 gene increases with age. SMNs are the most common cause of mortality in survivors of bilateral disease. Patients with family history of RB have a higher cumulative incidence of second neoplasms compared with bilateral RB children without a family history. Patients with sporadic RB are not at increased risk. For hereditary retinoblastoma, the greatest risk is neoplasms of bone (osteosarcoma), connective and soft tissue (leiomyosarcomas), eye, orbit, and nasal cavities. Patients also have increased risk of developing pineoblastoma, melanoma, CNS malignancies, and neoplasms of buccal cavity and uterus. The lowest risk is for neoplasms of lung, breast, and colon [67]. The median age at diagnosis of second neoplasm is 15–17 years. Survivors of a second neoplasm appear to have an increased risk of third and fourth malignancy that occurs at shorter intervals. Cumulative incidence of the third neoplasm is 22% at 10 years from the diagnosis of second cancer and it occurs at a median of 5.8 years [68].

Radiation results in an increased incidence of second cancers especially in patients with hereditary RB. The cumulative probability of developing SMN in patients with germline RB1 gene mutation is 38% when treated with radiation versus 21% without radiation. Children receiving radiation during their first year of life have a higher risk of developing SMN. The risk of therapy-related leukemia is minimal as the cumulative doses of etoposide and other topoisomerase inhibitors used in the treatment of RB are relatively low.

11.2 Impaired Orbital Growth

As children develop RB at a young age and orbital growth is still in progress, enucleation and/or orbital irradiation results in orbital growth impairment as the child reaches adolescence ('hourglass' facial deformity). Final orbital volumes after enucleation depend on the size of the orbital implant. In bilateral RB, the goal of therapy is to delay radiation that may allow more complete orbital and facial growth [69].

11.3 Visual Outcome

Visual outcome correlates with the intraocular stage and tumor location. Visual acuity of 20/40 or better can be achieved in 90% of eyes with tumors away from the macula and in 24% of eyes with macular tumors [70, 71]. Since RB affects the visual system at an early age when CNS is still developing, the final visual outcome is determined by the extent of the disease itself and/or treatment-induced damage in the visual pathways.

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Rare Pediatric Tumors

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and Girish Chinnaswamy

Abbreviations

ACC	Adrenocortical carcinoma
DHEA-S	Dehydroepiandrosterone sulfate
DSRCT	Desmoplastic small round cell tumor
HiPEC	Hyperthermic peritoneal perfusion
LFS	Li–Fraumeni syndrome
NPC	Nasopharyngeal carcinoma
PPB	Pleuropulmonary blastoma
TNM	Tumor–node–metastasis
UESL	Undifferentiated embryonal sarcoma of liver

1 Definition, Incidence and Caveats

Current data puts the global incidence of childhood cancer in children aged 0–14 years to be 140.6 per million years [1]. Pediatric cancer in itself is thus a rare disease. Several pediatric oncology investigative groups across the globe have defined which tumor qualifies to be under the rubric of "rare pediatric tumor."

1. TREP (Tumori Rari in Eta Pediatrica) [2]: Italian collaborative group formed in 2000, defined pediatric very rare tumors (VRTs) as "any malignancy characterized by an annual incidence of <2/million in population up to 18 years." Based on this, they identified 297 patients over a 5-year period across 45 centers in Italy. Liver tumors weren't included in this group as they were being studied by the SIOPEL group. Also, germ cell tumors (GCTs), retinoblastomas, rare nonrhabdomyosarcoma (RMS) soft tissue sarcomas also were excluded as they had their own therapy protocols.
2. Rare Tumor Working Group (UK Children's Cancer & Leukemia Group) [3]: Rare tumor was defined as age-standardized annual incidence of less than 1/million children in the UK. Melanomas and GCTs were excluded. Between 1991 and 2000, 766 cases were recorded, which comprised of 5% of all childhood cancers.
3. German Childhood Cancer Registry (GCCR) [4]: Retrospective audit conducted between 2001 and 2010; any tumor having an incidence of <0.3% of all malignancies were defined as rare. Overall, 232 patients were identified in children less than 15 years.
4. European Cooperative Study Group for Pediatric Rare Tumors (ExPERT) [5]: Formed in 2008, by collaboration of groups from Italy (TREP), UK, Germany (GCCR), France (FRACTURE) and Poland. Defines rare tumor as "any solid malignancy or borderline tumor characterized by an annual incidence of <2/million and/or not already considered in clinical trials." This definition encompasses both the epidemiological (defined by incidence) and clinical (rare adult cancers that may arise in childhood) aspects of rare cancers. Since then, the ExPERT group has published incidence rates and treatment outcomes on selected tumor groups [6–10].
5. Infrequent Tumor Working Group–Children's Oncology Group (COG) [11]: In order to streamline the enrollment of rare tumors and make the group more qualitative, numerical cut-off was dropped from the criteria and instead defined rare tumor as "other malignant epithelial neoplasms and melanomas" in the International Classification of Childhood Cancer subgroup 11 of the SEER Database. While including thyroid cancers and melanomas (excluded by previous groups), this definition excluded pancreatoblastoma (PB) and pleuropulmonary blastoma (PPB).

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Despite the efforts to classify rare tumors under a single umbrella, several hurdles exist in extracting prognostic and therapeutic data on these tumors. These “orphan diseases” may be inappropriately classified, diagnosed and treated. Coding errors may inadvertently misclassify these diseases under adult oncology registries because of their higher prevalence in the adult age group [12].

The COG Every Child Project represents a new approach to support clinical and biologic research for rare tumors and will allow identification of patients, submission of biologic specimens, and provide status updates for children seen at a COG institution [13].

2 Profiles of Rare Tumors

Covering the entire gamut of pediatric rare tumors is beyond the scope of this chapter. While the entire list is outlined in Table 1 [14, 15], important tumors among these are described below.

Table 1 List of rare tumors in children

System involved	Type of cancer
Head and neck region	*Nasopharyngeal cancer*
	Esthesioneuroblastoma (olfactory PNET)
	Thyroid tumors
	Oral cavity cancer
	Salivary gland tumors
	NUT midline carcinoma
Thoracic cancers	Breast cancer
	Tracheobronchial tumors
	Pleuropulmonary blastoma
	Esophageal cancer
	Thymoma and thymic carcinoma
	Cardiac tumors
	Mesothelioma
Abdominal cancers	*Adrenocortical carcinoma*
	Gastric cancer
	Pancreatoblastoma
	Desmoplastic small round cell tumor (DSRCT)
	Colorectal cancer
	Gastrointestinal carcinoid
	Gastrointestinal stromal tumor (GIST)
Genital/urinary cancers	Bladder cancer
	Nongerm cell gonadal tumors
	Cervical and vaginal cancer
Other rare tumors	Multiple endocrine neoplasia (MEN) and carney complex
	Pheochromocytoma and paraganglioma
	Melanoma
	Nonmelanomatous skin cancer
	Chordoma

2.1 Nasopharyngeal Carcinoma

2.1.1 Epidemiology

Accounting for 35–50% of all nasopharyngeal cancers, nasopharyngeal carcinoma (NPC) is relatively rare in children, with only 1% of all cases occurring in less than 19 years. It is an endemic cancer with a higher prevalence in well-defined ethnic groups in Hong Kong, China and Alaskan Eskimos [14]. It shows bimodal age distribution with an early peak at 10–20 years and a late peak at 40–60 years.

2.1.2 Risk Factors

1. Epstein–Barr virus infection: EBV is strongly associated with NPC. Apart from its oncogenic potential (described below in pathogenesis; Fig. 1), circulating levels of EBV-DNA and serological documentation of EBV-DNA infection may aid in the diagnosis [16].
2. HLA subtype: HLA A2Bsin2 haplotype is associated with a higher risk of NPC [17].

2.1.3 Histology and Pathogenesis

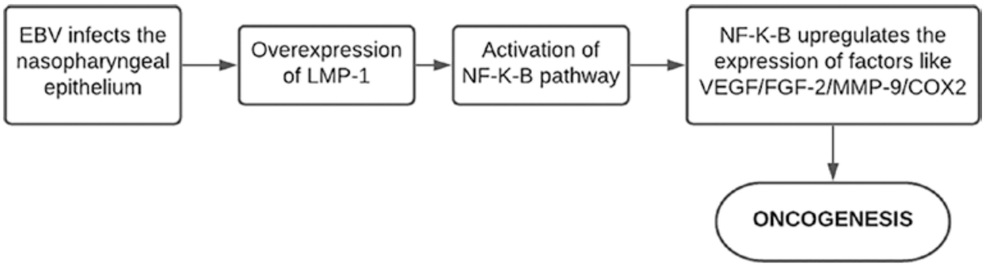
NPC originates from the surface epithelium of the fossa of Rosenmüller and can be categorized into three distinct histological subtypes.

- Type I (sporadic): Keratinizing squamous cell carcinoma similar to other cancers of the head and neck region. Etiologically, this is related to alcohol and tobacco exposure and is more common in adults.
- Type II: Nonkeratinizing variety of SCC. It is further subclassified into IIa and IIB on the basis of lymphoid infiltration.
- Type III (endemic): Undifferentiated variety. It is the most common subtype seen in childhood NPC. It is secondary to virological/environmental risk factors and genetic susceptibility. It is more common in children and almost universally associated with EBV infection.

2.1.4 Clinical Presentation

- Usually presents in the second decade of life (13–15 years) with a male preponderance.
- In comparison to adults, children have larger primaries, present with a more advanced disease and higher nodal stage. Despite this, children overall have a better prognosis.
- Symptoms are related to local spread and distant metastases.
- Local spread: epistaxis (unilateral > bilateral), congestion, otitis media, trismus
- trotter’s triad: triad of conductive deafness (due to Eustachian tube block), ipsilateral temporoparietal neu-

Fig. 1 Step-wise oncogenesis secondary to EBV infection in the nasopharyngeal mucosa


EBV infects the nasopharyngeal epithelium
Overexpression of LMP-1
Activation of NF-K-B pathway
NF-K-B upregulates the expression of factors like VEGF/FGF-2/MMP-9/COX2
ONCOGENESIS

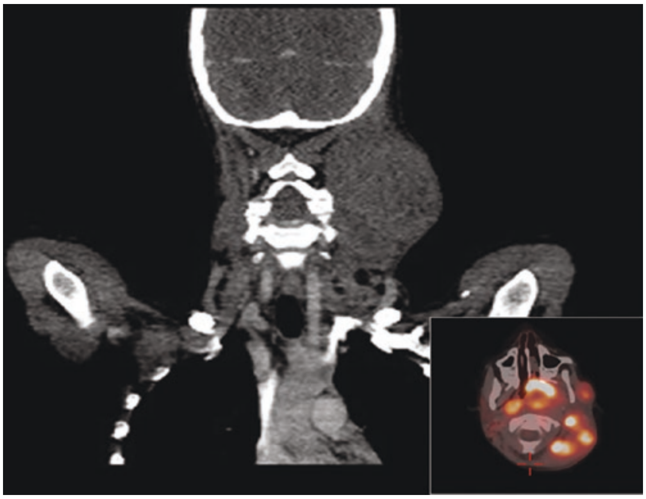


Fig. 2 Coronal view showing a large cervical nodal mass with inset showing PET avidity in both the nasopharyngeal and neck regions

ralgia (due to trigeminal nerve involvement) and ipsilateral palatal paralysis (due to vagus nerve damage).

- Skull-base erosion causes severe headache.
- Bilateral bulky nodes can occur in 80% patients and may be the only presenting feature.
- Distant spread to bones, lungs and liver is not uncommon with up to 90% patients in endemic regions presenting with Stage III/Stage IV disease vis-à-vis in nonendemic regions where the incidence is 77% [18].

2.1.5 Diagnostic Work-Up

- Diagnostic nasal endoscopy + biopsy of the primary mass OR biopsy of the cervical lymph node
- MRI of the head and neck region extending to the supraclavicular region
- CT scan to define skull base erosion
- CT Chest to evaluate parenchymal metastases and mediastinal nodal disease
- If available, FDG-PET CT can be a single diagnostic modality for staging of disease (Fig. 2).
- Audiogram at baseline to document deficits and also on follow-up
- Thyroid function tests at baseline and at follow-up

2.1.6 Staging and Therapy

The tumor–node–metastasis (TNM) classification of the American Joint Committee on Cancer is used to determine the tumor stage.

In view of its inaccessible location and anatomical site, surgery has a limited role. Therapy of childhood NPC is with an "intent to cure." Treatment options are as follows:

1. **Radiotherapy** alone in early stage disease: In Stage I disease, radiotherapy alone is adequate treatment. Majority of children do not come under this category, and hence, concurrent chemoradiation or induction chemotherapy followed by definitive radiation is the treatment of choice [19].
2. **Combination Chemotherapy and Radiation**: Chemotherapy agents with best single-agent activity include methotrexate, cisplatin, bleomycin, 5-fluorouracil and carboplatin [14]. Some of the chemotherapy regimens that have been employed are:
    (a) **BEP:** Bleomycin 15 mg/m^2 IV bolus on Day 1 and 12 mg/m^2 as a 24-h infusion on Days 1–5; Epirubicin 70 mg/m^2 in a 1-h infusion on Day 1; Cisplatin 100 mg/m^2 in a 4-h infusion on Day 5.
    (b) **PF:** Cisplatin 100 mg/m^2 as a 4-h intravenous infusion on Day 1 OR 20 mg/m^2/day on Days 1–5; Fluorouracil 1 g/m^2 as a 24-h infusion on Days 1–5 (Leucovorin 25 mg/m^2 given for 6 days to potentiate 5-FU action).
    (c) **MPF:** Methotrexate 120 mg/m^2 as intravenous infusion on Day 1; Cisplatin 100 mg/m^2 in a 4-h intravenous infusion on Day 2; Fluorouracil 1 g/m^2 in a 24-h infusion on Days 1–5 (Leucovorin 25 mg/m^2 given for 6 days to potentiate 5-FU action).
    (d) **BMP:** Cisplatin 100 mg/m^2 as a 4-h intravenous infusion on Day 1 OR 20 mg/m^2/day on Days 1–5; Methotrexate 50 mg/m^2 as intravenous infusion on Days 1, 8, 15. Bleomycin 20 IU/m^2 IV bolus on Days 1, 8 and 15.

While the majority of American and European protocols use a combination of 5-FU and Cisplatin as chemotherapy, the authors' center uses a modified BMP regimen [20]. The survival outcomes of various groups in NPC are tabulated below in Table 2. Survival outcomes were comparable with European

Table 2 Survival outcomes of nasopharyngeal carcinoma treated by various cooperative groups

Group/Protocol	Chemotherapy regimen	Number of patients	Concurrent chemoradiation	EFS/OS
TREP project, Italy [21]	PF	46 children	Yes (cisplatin)	79.3%/80.9%
Rare Cancer Network (RCN) [22]	Multicenter study (70% protocols were CDDP-based)	165 (nonmetastatic)	Yes	68.8%/77.4%
Tata Memorial Hospital [20]	BMP	81 children	No	68%/73%
ARAR0331, Children's Oncology Group [23]	PF	111	Yes (cisplatin)	84.3%/89.2%
NPC-2003, German POH [24]	PF + interferon 1β	45	Yes (cisplatin)	92.4%/97.1%

Abbreviations: *PF* Cisplatin + 5-fluorouracil, *BMP* Bleomycin, methotrexate and cisplatin

data demonstrating a 5-year PFS/OS of 79.3%/80.9% [21] and the COG data showing 5-year EFS/OS of 84.3%/89.2% [23]. German investigators have used interferon 1β (100,000 IU/kg as iv infusion thrice a week for 6 months) after a Cisplatin–5FU backbone and have noted a EFS/OS of 92.4%/97.1% at a follow-up of 30 months [24]. The rationale for employing IF-1β is because of its putative antiviral activity against EBV. All these regimens used concurrent chemoradiation with Cisplatin during weeks 1 and 3 of RT.

2.1.7 Doses of Radiation

Nasopharyngeal carcinoma is a radiosensitive disease and RT is the primary modality of therapy. The regional nodes in the entire head and neck area are also irradiated and structures surrounding the nasopharynx and entire neck should also be irradiated [14]. Type III nasopharyngeal cancers are most radiosensitive.

Recommended doses for the primary site and other involved nodal sites range from 59.4 to 70 Gy (1.8–2 Gy per fraction) and some studies have shown improved local control when doses >66 Gy are used [22].

2.1.8 Late Effects

Common long-term morbidities seen in survivors of childhood NPC are neuroendocrine sequelae (encephalopathy, thyroid dysfunction and pituitary dysfunction), hearing deficits, oral and dental effects (xerostomia, dental malocclusion, glossolalia, trismus) and neck fibrosis.

All of these are RT dose related, and hearing deficits can be compounded due to the use of Cisplatin.

Cochlear sparing RT (limiting the dose to cochlea to 45 Gy), Parotid sparing RT, use of amifostine (to reduce xerostomia) are some of the approaches to reduce these late effects.

2.2 Pleuropulmonary Blastoma

2.2.1 Epidemiology

Pleuropulmonary blastoma (PPB) is an embryonal tumor arising from the thoracopulmonary mesenchyme, which occurs exclusively in toddlers and young children, presenting either as a parenchymal or pleural mass.

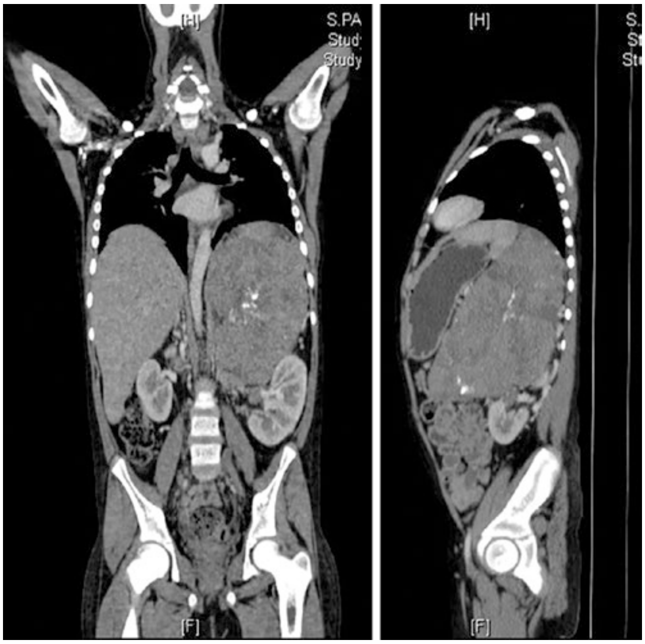


Fig. 3 Coronal and sagittal views of an adrenocortical carcinoma (well-demarcated lesion with stippled calcification)

PPB is strongly associated with germline mutations of DICER-1.

PPB is a rare tumor and the PPB registry forms an important source of information on the types and outcomes of this tumor [25].

2.2.2 Classification

PPBs are classified histologically as Type I, II and III as per Dehner's classification [26] with Type I being completely cystic, Type III being entirely solid (Fig. 3) and Type II representing a transition between the two. The clinical demographic and survival characteristics are outlined below (Table 3) [25]:

2.2.3 Prognostic Factors

- Complete resection at diagnosis is a favorable prognostic factor
- Doxorubicin containing regimens produced a better outcome in Type II/III PPBs.

Table 3 Clinical features of pleuropulmonary blastoma

	Type I	Type II	Type III
Histology	Purely cystic neoplasm with subtle malignant changes	Cystic and solid components	Purely solid with blastemal and sarcomatous components
Median age	8 months	35 months	40 months
Relative proportion	33%	35%	27%
Anaplasia	<10%	60%	70%
Distant metastases	<5%	7%	10%
DICER1 mutation	62%	63%	75%
5-year survival	89%–100%	71%	53%
Role of chemotherapy	Questionable if completely resected	Needs anthracycline-based chemotherapy	

- Type I fared better compared to Type II/III [7].

Across all the types of PPB, DICER1 mutation was noted in two-thirds of patients. Apart from PPB, DICER1 mutation is associated with a varied spectrum of solid tumors viz. cystic nephroma/Wilms tumor, sex cord stromal tumors, multinodular goiter, pinealoblastoma, medulloepithelioma, juvenile intestinal polyps and seminoma [27].

Role of DICER1: DICER1 encodes a 218 kD ribonuclease III endonuclease that participates in generation of mi-RNA. Mutated DICER1 or loss of DICER1 causes retention of abnormal mi-RNA sequences leading to disruption in branching morphogenesis and mesenchymal expansion [27]. Presence of germline DICER1 mutation has no prognostic impact on PPB.

In children with a known DICER1 pathogenic variant, clinical and radiographic screening guidelines for PPB (and other tumors) have been recommended [27]: Chest radiograph at birth and every 4–6 months until 8 years of age, yearly from 8 to 12 years of age. CT scan to be considered (with dose optimization) at 3–6 months of age. If mutation is detected after 12 years, a baseline chest radiograph or CT scan is recommended.

2.2.4 Clinical Features

Children present with nonspecific symptoms of fever, malaise and abdominal pain. Chest symptoms include respiratory distress, cough and pneumothorax.

The majority of lesions are right-sided (60%); one-third have bilateral disease.

Symptoms of distant spread include headache, irritability and vomiting. Cerebral metastases are frequent both at diagnosis and relapse, with a cumulative probability of 11% and 54% at 5 years for Type II and III PPB, respectively [28].

2.2.5 Diagnostic Work-Up

1. CT/MRI of the primary chest mass (see Fig. 3)
2. Bone scintigraphy by Tc99-diphosphonate
3. FDG-PET/CT scan (if available)—single diagnostic and staging modality
4. CT scan of head

2.2.6 Therapy

Complete surgical clearance (wedge excision, lobectomy or pneumonectomy) forms the cornerstone of cure. As per the histologic type, the PPB registry and ExPERT committee has demonstrated the following outcomes [7, 25]:

- Type I: Surgery is the treatment of choice with a 5-year DFS/OS of 82%/91%.
  - 10% may progress to Type II/Type III.
  - Adjuvant chemotherapy does not appear to have any impact on rate of progression.
- Type II/III: Sarcoma-like therapy with doxorubicin-based regimens
  - 5-year DFS/OS: Type II: 59%/71%; Type III: 37%/53%.
  - Approximately, half of these tumors relapsed in the CNS.

2.3 Adrenocortical Carcinoma

2.3.1 Epidemiology

Adrenocortical carcinoma (ACC) is a rare but aggressive endocrine neoplasm arising from the fetal zone of the fetal adrenal cortex. It has a bimodal age of distribution with peaks in the first and fourth decades with a female predilection [29]. A number of tumor syndromes are closely associated with ACC; notable among these are Li–Fraumeni syndrome (LFS), Beckwith–Weidemann syndrome, Carney complex, Lynch syndrome and MEN-1 [14].

Annual incidence in US is 0.2–0.3 cases/million. It is most prevalent in Southern Brazil. The reason for this clustering is a high prevalence of R337H germline mutation in the TP53 tumor suppressor gene [14]. Genomic landscape of ACC shows presence of IGF2 overexpression (most common genomic alteration), presence of TP53 mutations, ATRX mutations and beta-catenin mutations.

2.3.2 Clinical Features

The IPACRT registry and a single center study in southern Brazil provide valuable information on the clinical profile of ACC [30, 31].

Median age at diagnosis was 3.2 years with a female predilection. As it is a hormone secreting tumor, the clinical manifestations follow the nature of hormone secreted. The most common pattern is virilization (either isolated or in combination). Table 4 shows the clinical features, hormonal profile and the relative incidence of each [32]. Small secretory ACCs can potentially lead to endocrine manifestations and precede the onset of an abdominal lump. Certain scenarios must alert the clinician to the possibility of ACC in a child [32].

- To avoid delaying the diagnosis of ACC, the clinician should consider any child younger than 4 years with pubarche (pubic hair) to have ACC and refer early.
- Unexpected somatic growth in the context of an abdominal lump must point toward possibility of ACC.
- Presence of acne on an infant can be considered pathognomonic of an adrenocortical lesion.
- Cushing syndrome is very rare in children, it should be considered highly indicative of ACC in children younger than 10 years.

2.3.3 Diagnostic Work-up

- Elevated levels of urinary keto-steroids and plasma dehydroepiandrosterone sulfate (DHEA-S).
- Urinary DHEA concentration and 17-hydroxycorticoid levels are less sensitive.

These hormonal assays provide a clue to the diagnosis and also aid in monitoring after completion of therapy.

- MRI of the abdomen/CT abdomen can delineate the regional extent of the tumor (Fig. 4)
- CT Chest + bone scintigraphy for staging.
- FDG-PET/CT (not validated, but act as a single investigation to assess locoregional and distant spread).
- Staging of ACC is largely surgical, based on COG and takes into account tumor volume and resectability [32].
  - *Stage I:* Tumor totally excised, tumor size <100 g or 200 mL, absence of metastasis and normal hormone levels after surgery
  - *Stage II:* Tumor totally excised, tumor side >100 g or >200 mL, absence of metastasis and normal hormone levels after surgery
  - *Stage III:* Unresectable tumor, gross or microscopic residual tumor, tumor spillage during surgery, persistence of abnormal hormone levels after surgery, or retroperitoneal lymph node involvement
  - *Stage IV:* Metastatic disease

Table 4 Clinical spectrum of adrenocortical carcinoma

Clinical feature	Hormone	Frequency
Virilization Pubic and facial hair Clitoral hypertrophy Hoarseness of voice Accelerated growth	Dehydroepiandrosterone Androstenedione Dehydroepiandrosterone sulfate Testosterone	45%–50%
Mixed Symptoms of virilization and Cushing syndrome	2 or more hormones (increased cortisol and androgens)	45%–50%
Cushing syndrome Moon face, buffalo hump, hypertension	Cortisol Deoxycortisol	5%–8%
Nonfunctional Abdominal mass	Elevated adrenocortical hormones	5%–8%
Feminization (gynecomastia in males and pseudopuberty in females)	Estradiol, Estrone, Estriol	<1%
Conn syndrome	Aldosterone	<1%

2.3.4 Treatment

Treatment of ACC is surgery with the extent of surgical resection having a prognostic impact on the outcome. Chemotherapy is used in locally advanced and metastatic disease. Chemotherapy regimens consist of Cisplatin, Etoposide, Doxorubicin and Mitotane [33].

Mitotane (an insecticide derivative) a nonclassical antineoplastic agent, noted to cause adrenal necrosis in animals [3], has been used in combination with chemotherapy. But a narrow therapeutic window (requires drug monitoring with levels between 14 and 20 mg/L) and consequent serious side effects are issues that limit its efficacy [34].

The 5-year survival ranges from 70% to 80% in localized disease to 43%–65% in locally advanced disease and 10%–20% in metastatic disease [35]. Apart from conventional prognostic factors like tumor volume, extent of resection, presence of metastatic disease, overexpression of Ki-67 ligand (≥15%) is a strong prognostic indicator linked to adverse outcome [35]. A recent landmark phase II study in 39 patients with unresectable or metastatic ACC, explored the role of Pembrolizumab (anti-PD1 monoclonal antibody) at a dose of 200mg every 3 weeks, to assess objective remission rate. The disease control rate (percentage of patients who demonstrated objective response or stable disease) was 52% (95% CI, 33% to 69%). While most patients with objective responses in this study (78%) did not have Lynch syndrome and had microsatellite-stable (MSS) tumors, 2/6 (33%) of the MSI-high (MSI-H) or MMR-deficiency (MMR-D) tumors did demonstrate partial response [36]. Despite the study including mostly adults (median age: 19–87), it provides encouraging proof of role of targetted therapies in a group of tumors with otherwise poor survival rates. It also highlights the importance of testing patients of microsatellite instability and mismtach repair deficiency.

2.3.5 Follow-up

As nearly two-thirds of patients with ACTs are linked to genetic predisposition, referral to a cancer genetics department is mandatory for genetic counseling, screening for second neoplasms and family follow-up.

Regular surveillance with clinical examination, ultrasound abdomen, estimation of urinary/plasma hormone profiles are necessary to identify recurrence.

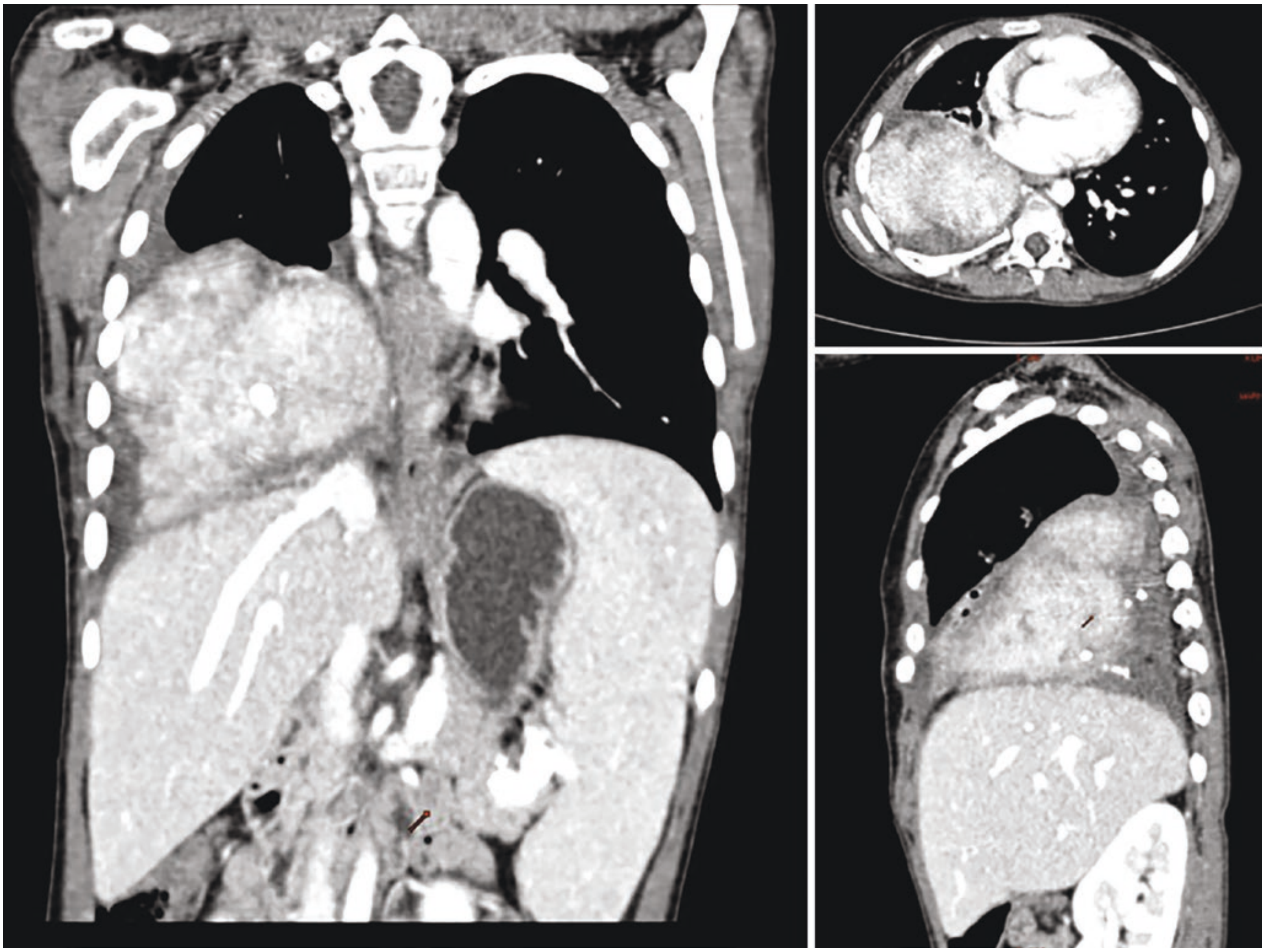


Fig. 4 CT thorax showing a completely solid lesion arising from the pleural surface suggestive of pleuropulmonary blastoma

2.4 Pancreatoblastoma

2.4.1 Epidemiology

Historically termed as "infantile carcinoma of the pancreas, pancreatoblastoma is the most common pancreatic tumor in young children and accounts for 10%–20% of all childhood pancreatic tumors." The clinicopathological features and treatment approaches mirror that of hepatoblastoma as both have an identical age group, common association with Beckwith–Weidman syndrome and FAP, common molecular drivers (CTNNB1 and IGF2 gene mutations), AFP as a tumor marker, similar chemotherapy backbone (cisplatin and doxorubicin) and surgery being the mainstay of therapy [3]. The genesis of PB is though to be the fetal pancreatic acinar cell.

2.4.2 Clinical Features

Nearly half of the cases arise from the head of pancreas. Upper abdominal pain, epigastric mass and gastric outlet obstruction can be presenting symptoms.

A third of patients develop metastatic spread to liver (via the portal circulation), lungs (haematogenous spread) and lymph nodes (lymphtaic) a third of patients can develop distant metastases, chiefly lungs [6].

Paraneoplastic syndromes due to secretion of ADH and ACTH can rarely occur [37].

2.4.3 Diagnostic Work-up

- Blood work including liver function tests and serum AFP (to be correlated with age as per nomograms) [38]
- Regional imaging with CT/MRI abdomen
- Staging with CT Chest or PET/CT scan. Bone scintigraphy can be used to screen for bone mets in centres where PET/CT is unavailable

2.4.4 Treatment

Akin to ACC, pancreatoblastoma is a surgical tumor with complete surgical excision the cornerstone of treatment. As most of the tumors involve the head of the pancreas, a Whipple procedure is the surgery of choice.

Because of its rarity, guidelines on chemotherapy are derived from collaborative groups. PB was in fact the first tumor to be reviewed by the EXPeRT committee to analyze the clinical findings and therapy outcomes [6].

For locally advanced and metastatic tumors, chemotherapy regimen consisting of cisplatin and doxorubicin is recommended (similar to PLADO regimen in hepatoblastoma). In a cohort of 20 patients, 18 received chemotherapy with a response rate of 73% and 5-year EFS/OS of 58.8%/79.4% [6].

2.5 Desmoplastic Small Round Cell Tumor (DSRCT)

2.5.1 Epidemiology

Overall, soft tissue sarcomas represent only 10% of all childhood cancers, of which DSRCT is the rarest member. Relatively new to the sarcoma family, it was first described by Gerald and Rosai at Memorial Sloan Kettering in 1989 [39], 9 years before its canonical EWS-WT1, t(11;22)(p13:q12) was identified [40]. DSRCT is a small blue round cell tumor that arises in the peritoneal cavity. It affects young patients in their second and third decade of life, with a striking male predilection.

2.5.2 Clinical Features

DSRCT is an aggressive sarcoma arising from the peritoneum and characterized by multifocal tumors and extensive locoregional spread [41].

Vague abdominal discomfort, pain and discomfort are the most common presenting symptoms. Coating of peritoneum with these tumors causes impaired resorption of peritoneal fluid leading to ascites. Tumor dissemination occurs most commonly to the liver and rarely to pleura, lungs, paratesticular region and supraclavicular lymph nodes [41].

2.5.3 Diagnostic Work-up

- Blood work including complete blood count and CA-125
- Biopsy of the lesion with demonstration of the characteristic translocation (EWS-WT1) is 100% confirmatory of DSRCT. Microscopy demonstrates nests of small blue round cells separated by desmoplastic stroma. Immunohistochemistry shows positivity for epithelial (keratin, EMA), mesenchymal (vimentin) and neural (NSE, CD99) markers. WT1 is positive in about 80%–90% DSRCT.
- Imaging: CT (computed tomography) scan of the thorax, abdomen and pelvis. Alternatively PET (positron emission tomography) -CT scan is increasingly being used as a single investigation for both local assessment and screening for distant metastasis and it is associated with a low negative predictive value.
- Two staging symptoms have been described: Peritoneal Cancer Index and MDACC staging system. The MDACC staging system is as below [41]:
  - Stage 1: Limited disease, localized to one or two sites in the abdomen or one site elsewhere.
  - Stage 2: Patients with any amount of extensive peritoneal disease;
  - Stage 3: Patients with liver metastasis and peritoneal disease
  - Stage 4: Patients with peritoneal and liver disease, as well as disease outside the abdominal cavity, including in the lymph nodes.

2.5.4 Treatment

DSRCT is treated on a multimodality regimen employing an Ewing sarcoma-like chemotherapy backbone with local therapy ranging from cytoreductive surgery, HiPEC (hyperthermic peritoneal perfusion), whole abdominal radiotherapy to stereotactic radiosurgery.

Chemotherapy regimens that have been tried are as follows*:

1. P6 regimen [42] (alternating courses of high-dose cyclophosphamide, doxorubicin, vincristine and ifosfamide-etoposide); response rate: 100%
2. Interval compressed VDC/IE [43] (Ewing sarcoma regimen); response rate: 68.4%
3. Standard VDC/IE; response rate: 48.2%
4. Addition of irinotecan-temsirolimus to the VDC/IE compressed regimen; response rate: 50% [44]

* please note that %s indicate the response rate. Despite aggressive and multimodality therapy, DSRCT is a group of tumors associated with dismal survival rates, with 5-year OS at 30%–40%.

2.6 Undifferentiated Embryonal Sarcoma of the Liver

2.6.1 Epidemiology

Historically termed as malignant mesenchymoma and fibromyxoma of the liver, undifferentiated embryonal sarcoma of liver (UESL) was known by its current term in 1978 [45]. An aggressive sarcoma, it is the third most common pediatric liver tumor (after hepatoblastoma and hepatocellular carcinoma) with a median age of 10.5 years and equal gender predilection [46].

2.6.2 Clinical Features

UESL presents as an abdominal lump and nonspecific symptoms of fever, nausea and anorexia in older children. Rhabdomyosarcoma (RMS) of the biliary tract is a close differential and several clinicopathological differences have been

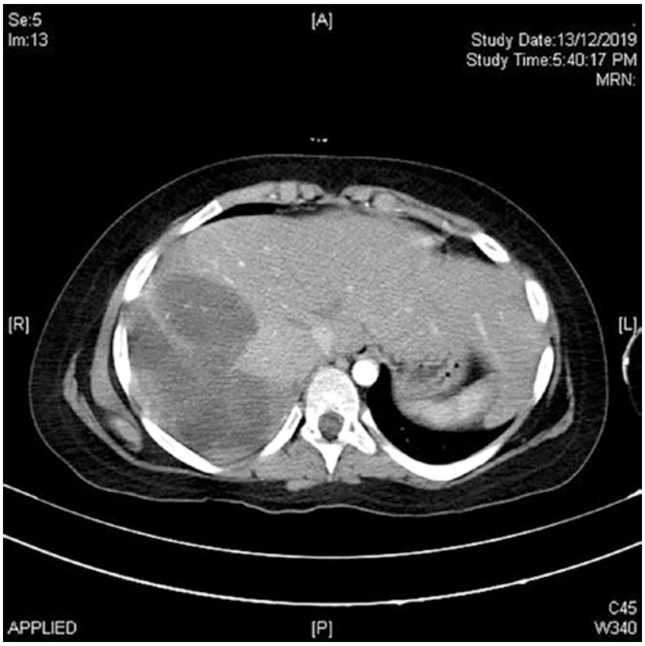


Fig. 5 Atypical lesion of UESL; a cystic lesion with necrosis within, arising from right lobe of the liver

described between the two [46]. An older age of onset, absence of obstructive symptoms like jaundice at presentation and location in the right lobe characterize UESL more than RMS (Fig. 5). Additionally, on IHC, UESL stains negative for myogenin and myoD1. Cytogenetic evidence of chromosomal breakpoint at 19q(13.4) (also present in hepatic mesenchymal hamartoma) also aids in differentiating this from RMS. An ultrasonography demonstrates the cystic/mixed nature of the swelling.

2.6.3 Treatment and Outcomes

Surgical resection with or without chemotherapy is the choice of treatment in children. It is a chemosensitive tumor with alkylating-based regimen with or without anthracyclines forming the front-line therapy with carboplatin-etoposide as second-line therapy [47]. The 5-year overall survival is quite impressive and ranges between 72%–80% [47–49].

Despite its chemosensitivity, inability to achieve complete clearance of all tumor sites portends a poor prognosis. Orthotopic liver transplantation is a viable method of attaining local control in tumors, which would otherwise be unresectable [49].

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Childhood and Adolescent Extracranial Germ Cell Tumors

Subramaniam Ramanathan and Maya Prasad

Abbreviations

AFP	Alpha-fetoprotein
AUC	Area under the curve
BEP	Bleomycin, etoposide and cisplatin (weekly bleomycin)
BIP	Bleomycin-induced pneumonitis
GCT	Germ-cell tumor
GFR	Glomerular filtration rate
HBCR	Hospital-based cancer registry
LDH	Lactate dehydrogenase
PEb	CISPLATIN, Etoposide, bleomycin (3-weekly bleomycin)
PGC	Primordial germ cell
RPLN	Retroperitoneal lymph node
RT	Radiation therapy
SCT	Sacrococcygeal tumor
β-HCG	Beta-human chorionic gonadotropin

1 Introduction

Germ-cell tumors (GCTs) are a rare, heterogeneous group of tumors arising from the primordial germ cells with a favorable survival, even in advanced stages. GCTs arise from molecular defects in primordial germ cells (PGCs) in the gonads. PGCs are totipotent in nature with an ability to differentiate to all three germ layers and extraembryonic tissues. Migration of PGCs from the yolk sac through the midline of the developing embryo happens at around third week which is governed by strict temporospatial expression of chemomediators like CXRC4 and CXCL12 [1]. Aberrant migration of these cells along their course explains the proclivity for extragonadal GCTs to occur in midline.

Multidisciplinary approach over a backbone of platinum-based chemotherapy has dramatically improved survival in pediatric extracranial germ-cell tumors. Recent efforts to achieve better outcomes are directed toward harmonization of risk stratification across various groups and reducing therapy in favorable risk groups to minimize treatment related toxicity.

2 Incidence and Epidemiology

Extracranial germ-cell tumors constitute about 3% of all the pediatric malignancies (age <15 years) and display a bimodal distribution [2]. This increases to about 14% at onset of puberty (15–19 years), making it the most common solid tumor, and the second most common malignancy after Hodgkin's lymphoma in adolescents of both genders [3]. Data from the SEER database suggests the age-adjusted incidence of extracranial germ-cell tumors in the United States to be 11.7 per million in boys and 6.7 per million in girls [4]. Data on incidence in India is lacking because of poor reporting and inaccurate staging. A recent hospital-based cancer registry (HBCR) reported the incidence of GCTs to be 1.6–3.6% in boys and 0.8–4.5% in girls among all childhood cancers [5]. A single-center cross-sectional review in Indian children reports the annual incidence of GCTs to be 11.4% among all pediatric solid tumors with an equal gender predilection. The gonadal tumors were commonly seen in females above 10 years of age, while the extragonadal tumors were more commonly seen in children <4 years [6].

A number of clinical risk factors do exist (some with conflicting evidence) like presence of cryptorchidism, maternal estrogen levels during pregnancy, parental lifestyle, higher birth weight but none of the studies have been adequately powered to be assigned an attributable risk [7]. In adults, a positive family history is elicitable in 1–3% of cases of GCT [8, 9]. Such an association has not been found in pediatric GCTs [7].

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3 Clinical Presentation

Clinical presentation including signs and symptoms of GCTs are dictated by its location (extragonadal or gonadal) and regional extent. Distant metastatic disease is usually present in 20% with lungs being the most common site [3]. The clinical presentation of GCTs across all locations is summarized in Table 1.

Testicular GCTs are usually painless and presence of pain usually indicates benign etiologies like epididymo-orchitis or torsion. Ovarian GCTs however are associated with pain in 85% cases. Extragonadal GCTs depending on the site can have varied presentations depending on its site. Extragonadal GCTs can occur in sacrococcygeal, retroperitoneal, mediastinal and other atypical locations.

Sacrococcygeal tumors (SCTs), much more common in females than males, present in early infancy until about 4 years of age, with a varying histological subtype (teratomas in the perinatal period and malignant GCTs in early childhood). Depending on the extent of internalization or externalization (with respect to the pelvic cavity) of the primary lesion, Altman classified SCTs from Type I-IV; Type I being completely external and Type IV being entirely internal (Fig. 1) [10]. Nearly 18% of SCTs in this cohort had associated congenital anomalies. Presacral tumors that are predominately internal present later in infancy through 4 years of age. Usual presenting symptoms of an internal lesion are either constipation or a buttock/abdominal mass; probability is quite high that these lesions are malignant [11]. Indian studies, albeit in small populations have shown a similar distribution [12, 13].

Table 1 Clinical presentation of germ-cell tumors (GCTs)

Testicular	Ovarian	Extragonadal
• Presents as a unilateral painless swelling. • Late presentation in developing countries can present as enlarged retroperitoneal lymph nodal mass in the abdomen • *Differentials* include: Paratesticular rhabdomyosarcoma, leukemic infiltration of the testis • Presence of pain indicates acute benign etiologies like torsion testis or epididymo-orchitis • *Children < 4 years:* Yolk sac tumors and immature teratomas are more common • *Children > 4 years:* Seminomas and mixed malignant GCTs are more seen	• Palpable abdominopelvic mass with abdominal pain in 85% patients • Rare accompanying clinical features include fever (10%), vaginal bleeding (10%) and isosexual precocity related to elevated beta-HCG • Unlike testicular tumors, histological subtype does not have any age correlation • *Differentials* include: Monodermal tumors (carcinomas), sarcomas, PNET • Rarely, Burkitt lymphoma can present as bilateral ovarian masses, bowel thickening and ascites	• *Sacrococcygeal:* Swelling over the back near the natal cleft with internal extension into the pelvis depending on subtype • *Mediastinal:* Anterior mediastinal mass with features of superior mediastinal syndrome in advanced cases • *Retroperitoneal:* Abdominal swelling with mass effect on adjacent organs with associated obstructive uropathy. Large masses can impinge on diaphragm causing respiratory distress • *Rare sites:* Vagina, orbit, adrenal • *Intracranial GCTs:* GCTs can occur in intracranial location also, most commonly in the pineal region; clinical presentation and management of intracranial GCTs have been dealt elsewhere

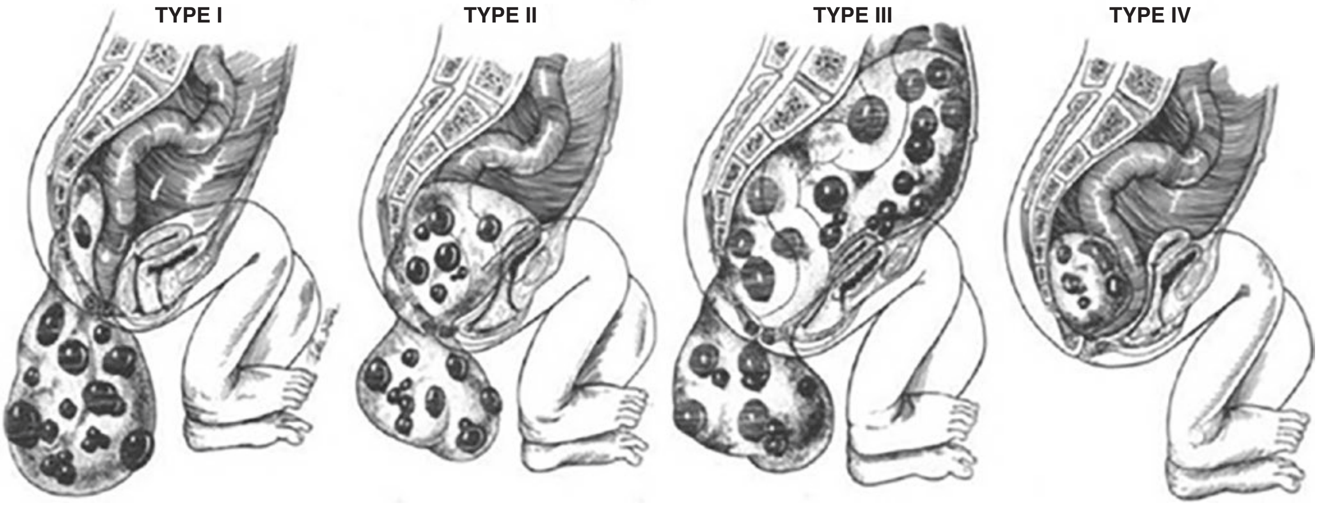

Fig. 1 Altman classification of sacrococcygeal teratoma. Reproduced with permission from Altman RP, Randolph JG, Lilly JR. Sacrococcygeal teratoma: American Academy of Pediatrics Surgical Section Survey-1973. J Pediatr Surg. 1974;9(3):389–98

Mediastinal GCT in an adolescent male could be the presenting feature of Klinefelter syndrome. Lymphoma/T-cell leukemia often presents with anterior mediastinal masses; short history, presence of effusion and negative tumor markers help in differentiating this more common condition from mediastinal GCTs. In a COG study on malignant mediastinal GCTs, younger patients presented with respiratory complaints (mostly teratomas) while older children had chest pain, precocious puberty and facial fullness [14], which also contained more yolk sac elements.

4 Evaluation and Work-Up

4.1 History and Clinical Examination

4.1.1 Tumor Markers

Alpha-fetoprotein (AFP), a glycoprotein synthesized in the fetal liver and yolk sac, is elevated in about 70% nongerminomatous GCTs. Even immature teratomas can have elevated AFP because of microscopic yolk sac elements. Age-adjusted values as per nomograms (Table 2) assist in identifying pathological elevation of AFP [15]. Childhood neoplastic conditions apart from GCTs that cause elevated AFP of varying magnitude include hepatoblastoma, hepatocellular carcinoma and hemangioendothelioma. β-Human chorionic gonadotropin (β-HCG), a peptide hormone synthesized by the developing embryo soon after conception and later by the placenta (syncytiotrophoblast), is seen to be elevated in tumors arising from extraembryonic tissues, like choriocarcinoma and rarely in dysgerminoma/seminoma. Raised β-HCG can also be seen in hepatoblastoma, neuroendocrine tumors, gestational trophoblastic diseases and pregnancy [16]. Other tumor markers like inhibin and lactate dehydrogenase (LDH) can be elevated in granulosa cell tumors and dysgerminomas, respectively. While the prognostic significance of elevated tumor markers (especially AFP) at presentation and its serial decline in adult population is well established [17, 18] studies in pediatric GCTs have failed to replicate this observation [19]. Lack of favorable decline in AFP however has been used as a criterion for upstaging the completely resected gonadal GCTs from Stage I to Stage II in the COG staging system (described later).

Table 2 Normal levels of serum alpha-fetoprotein [15]

Age (months)	Mean αFP (ng/mL)	αFP 95% range (ng/mL)
0	41,687	9120–190,546
1	36,391	7943–165,959
2	31,769	6950–144,544
3	27,733	6026–125,893
4	24,210	5297–109,648
5	21,135	4624–96,605
6	18,450	4037–84,334
7	16,107	3524–73,621
8–14	9333	1480–58,887
15–21	3631	575–22,910
22–28	1396	316–6310
29–45	417	30–5754
46–60	178	16–1995
61–90	80	6–1045
91–120	36	3–417
121–150	20	2–216
151–180	13	125–129
181–720	8	0.8–87

4.1.2 Imaging

It is a radiological evaluation of the locoregional extent of disease (ultrasound for testicular lesions and MRI/CT for other sites; noncontrast CT of chest). While presence of fat and bony elements defines teratomas, it is rare in seminoma/dysgerminoma which are more uniformly lobulated masses with interdividing septae. Secretory GCTs (yolk sac tumors, mixed GCTs and choriocarcinomas) are characterized by presence of irregular margins, necrosis and occasionally hemorrhage. Clinical symptoms must prompt bone-scan for evaluating metastases if any. MRI of brain should be obtained in all cases of choriocarcinoma [3].

4.2 Histopathological Examination

Broadly, GCTs are classified into teratomas (immature and mature) and malignant GCTs (yolk sac tumor, germinoma, embryonal carcinoma and choriocarcinoma).

Teratomas are well-demarcated solid-cystic masses, which harbor elements from all three germ layers, viz., hair, fat, teeth, sebaceous and keratinous material. While mature teratomas contain well-differentiated elements, immature teratomas show presence of fetal/embryonal counterparts of the same, most commonly neuroectodermal tissue and cellular mesenchyme. On the basis of immature neuroectodermal tissue, Norris et al. classified these into Grade 1–3 (Grade 1: rare foci ≤1/low power field; Grade 2: multiple foci ≤3/low power field; Grade 3: ≥4/low power field) [20]. Unlike in adults, prognostic relevance of grading on outcomes (inferior outcome with increasing grade) has not been described in children [21, 22].

Among the malignant GCTs, yolk sac tumor/endodermal sinus tumors are the most common variety. These are characterized by round to polygonal cells with a high nuclear-to-cytoplasmic ratio, with presence of Schiller-Duval bodies (sinusoidal structures with a central vascular core and a peripheral rim of flattened tumor cells). On IHC, they stain positive for AFP, cytokeratin, glypican-3 and Lin-28.

Seminoma/dysgerminoma is an umbrella term used for similar looking tumors in testis and ovary respectively. Analogous tumors in extrangonadal/intracranial locations are termed as germinomas. They are characterized by sheets of large, monotonous cells with prominent nucleoli, separated by fibrovascular septae with lymphoplasmacytic infiltrate. On IHC, they stain positive for Lin-28, PLAP and c-kit but are negative for AFP/β-HCG.

Isolated embryonal carcinomas are rare in children and usually one of the components in a malignant mixed germ-cell tumor. They are characteristically positive for CD-30 on IHC and stain negative for EMA, CEA and vimentin.

In practice, radiologically compatible lesions with unequivocal elevation of tumor markers obviate the need for a biopsy prior to starting definitive chemotherapy. In such inoperable cases, a second look surgery can be performed after 2–4 cycles of neoadjuvant chemotherapy, with the post-operative specimen revealing mostly mature teratomatous elements.

4.2.1 Role of Micro-RNAs [23]

Although tumor markers provide a practical and effective method of both diagnosis and monitoring during treatment of GCTs, their utility is limited to secretory GCTs. Nonsecretory GCTs (NSGCTs, embryonal carcinomas and teratomas) hence demand novel biomarkers.

Micro-RNAs are short, nonprotein-coding RNAs that are released into the bloodstream from cancer cells (within exosomes). Micro-RNAs from two “clusters,” miR-371–373 and miR-302–367, are overexpressed in all malignant GCTs, regardless of age, site and histopathological subtype [23]. Because they remain undegraded in circulation, micro-RNAs might be useful in diagnosis, disease monitoring and prognostication of malignant GCTs.

5 Principles of Management

Following the above investigations, GCTs are staged and risk-stratified for treatment. Universally the COG staging is employed in children; this is a surgical staging which varies as per site of primary tumor (Table 3) [24]. While the staging has strong surgical principles, a key feature is the incorporation of AFP measurement into this staging system. The importance of evaluating AFP before starting any treatment and its serial measurement (has bearing on staging) cannot be overemphasized. Although the risk strata widely vary across different study groups, the present philosophy is to *decrease therapy in favorable risk groups* to minimize long-term toxicity and *intensify therapy in advanced stage disease*. A recent review succinctly puts forth the notion of a more functional classification [3], where low-risk tumors can only be observed after surgical resection, intermediate-risk tumors can be given less chemotherapy while still achieving a comparable outcome and high-risk tumors be treated with newer effective regimens. To systematize the risk stratification taking into account all possible prognostic factors in pediatric GCTs, data from seven GCT trials were pooled, based on which a new evidence-based risk stratification for pediatric GCTs was formed. The analysis identified a group of patients aged ≥11 years with either stage III to IV extragonadal tumors or stage IV ovarian tumors with an inferior survival. In addition, Stage III/IV testicular tumors in children ≥11 years with IGCCC (International Germ Cell Consensus Classification)—intermediate/poor risk were also identified as poor performers. All these groups are now stratified as Poor Risk in the new risk stratification. The Standard Risk group has been subdivided into Standard Risk—1 and Standard Risk 2 based on age as previously mentioned [19]. The current multicenter AGCT1531 trial is employing this contemporary risk stratification [25].

5.1 Surgical Management [26]

5.1.1 Surgical Management of Testicular Tumors

High-inguinal radical orchiectomy (ligation of all cord structures at the level of the internal inguinal ring) should be the surgical approach for a scrotal tumor. In rare occasions, such as a prepubertal boy with a proven teratoma with no biochemical/radiological disease elsewhere, focal enucleation is adequate. In the event of scrotal violation, patient continues to be in stage I if tumor capsule remains intact and tumor markers decline appropriately. If the cord structures show evidence of tumor spread, the patient should be upstaged to stage II. A trans-scrotal biopsy however warrants a completion orchiectomy following upstaging to Stage II. Hemiscrotectomy is not required. Routine retroperitoneal lymph node (RPLN) dissection is not required. While children with RPLN of size >2 cm on baseline imaging and RPLN <2 cm coupled with elevated AFP are stratified as Stage III, children with presence of RPLN measuring 1–2 cm with normal AFP warrant a repeat imaging ±RPLN biopsy for appropriate staging.

5.1.2 Surgical Management of Ovarian Tumors [27]

Open surgical resection is recommended. The following guidelines are advocated by COG: (a) collection of peritoneal fluid or washings for cytology (b) examination of peritoneal surfaces with biopsy of any abnormal areas; (c) palpation of retroperitoneal lymph nodes; biopsy only if abnormal (firm or enlarged); (d) inspection of omentum; biopsy only if abnormal; (e) palpation/inspection of opposite ovary; biopsy only if abnormal; (f) Complete resection of involved ovary intact (no capsule entry on field) with sparing of fallopian tube if not involved. For bilateral ovarian tumors, wedge biopsy of one should be performed and the patient should have second look surgery after neoadjuvant chemotherapy, which would preferably be a fertility preserving surgery.

Table 3 COG staging of pediatric GCTs [24]

Testicular	
I	(1) Tumor limited to testis (testes) with negative microscopic margins, completely resected by high inguinal orchiectomy; (2) Tumor capsule cannot have been violated by needle biopsy, incisional biopsy or tumor rupture. Patients who have undergone scrotal orchiectomy without violation of the tumor capsule and with removal of the spermatic cord to the level of the internal ring are stage I. Patients who have undergone excisional biopsy for frozen section analysis with complete orchiectomy and cord excision at the same operation can be designated stage I. (3) No clinical, radiographic or histologic evidence of disease beyond the testes. (4) Lymph nodes all <1 cm maximum short-axis diameter on multiplanar imaging
II	(1) complete orchiectomy with violation of the tumor capsule in situ (includes preoperative needle biopsy and incisional biopsy or intraoperative tumor capsule rupture); (2) microscopic disease in scrotum or high in spermatic cord (<5 cm from proximal end). Failure of tumor markers to normalize or decrease with an appropriate half-life; (3) lymph nodes negative
III	(1) retroperitoneal lymph node involvement, but no visceral or extra-abdominal involvement; (2) lymph nodes ≥2 cm or lymph nodes >1 cm but <2 cm on short axis by multiplanar imaging CT that fail to resolve on reimaging at 4–6 weeks
IV	(1) distant metastases, including liver, lung, bone and brain
Ovarian	
I	(1) ovarian tumor removed without violation of the tumor capsule; (2) no evidence of partial or complete capsular penetration; (3) peritoneal cytology negative for malignant cells; (4) peritoneal surfaces and omentum documented to be free of disease in operative note or biopsied with negative histology if abnormal in appearance; (5) lymph nodes all <1 cm by short-axis diameter on multiplanar imaging or biopsy proven negative
II	(1) ovarian tumor completely removed but with preoperative biopsy, violation of tumor capsule *in situ* or presence of partial or complete capsule penetration at histology; (2) tumor >10 cm removed laparoscopically; (3) tumor morcellated for removal so that capsule cannot be assessed for penetration; (4) peritoneal cytology must be negative for malignant cells; (5) lymph nodes, peritoneal surfaces and omentum documented to be free of disease in operative note or biopsied with negative histology if abnormal in appearance
III	(1) lymph nodes ≥2 cm or lymph nodes >1 cm but <2 cm on short axis by multiplanar imaging CT that fail to resolve on reimaging at 4–6 weeks; (2) ovarian tumor biopsied or removal with gross residual; (3) positive peritoneal fluid cytology for malignant cells, including immature teratoma; (4) lymph nodes positive for malignant cells, including immature teratoma; (5) peritoneal implants positive for malignant cells, including immature teratoma
IIIX	Patients otherwise stage I or II by COG criteria but with the following: (1) failure to collect peritoneal cytology; (2) failure to biopsy lymph nodes >1 cm on short axis by multiplanar imaging; (3) failure to sample abnormal peritoneal surfaces or omentum; or (4) delayed completion of surgical staging at a second procedure for patients who had only oophorectomy at first procedure
IV	(1) metastatic disease to the parenchyma of the liver (surface implants are stage III) or metastases outside the peritoneal cavity to any other viscera (bone, lung or brain) and pleural fluid with positive cytology
Extragonadal	
I	(1) complete resection at any site, including coccygectomy for sacrococcygeal site; (2) must have negative tumor margins and intact capsule; (3) for any tumors involving abdominal cavity or retroperitoneum, peritoneal fluid or washings must be done for cytology and be negative for malignant cells; (4) lymph nodes ≤1 cm by imaging of abdomen, pelvis and chest
II	(1) microscopic residual disease; (2) gross-total resection with preoperative biopsy, intraoperative biopsy, microscopic residual disease or pathologic evidence of capsular disruption; (3) lymph nodes negative by abdomen, pelvic and chest imaging. Peritoneal fluid negative
III	(1) Gross residual disease or biopsy only; (2) lymph nodes positive with tumor resection. Lymph nodes ≥2 cm or lymph nodes >1 cm but <2 cm on short axis by multiplanar imaging CT that fail to resolve on reimaging at 4–6 weeks
IV	Distant metastases, including liver, lung, bone and brain

5.1.3 Surgical Management of Sacrococcygeal Tumors

The behavior of SCTs differs by age; 90% of neonatal SCTs are benign with the proportion of malignant tumors increases with age. Despite this difference, the surgical objective is to achieve a complete excision (including en-bloc resection of coccyx) with negative margins [27]. Because the tumor configuration beyond the neonatal period is more likely to have an internal component close to pelvic structures, upfront resection must be gauged against possible long-term gastrointestinal, genitourinary and neurological sequelae [28]. Literature also suggests to define the extent of neurologic, gastrointestinal and genitourinary dysfunction before any intervention so as to categorize any impairment of function at baseline and after surgery [29]. Also, delayed resection in SCTs did not adversely impact the outcome in published studies [30, 31]. In light of these observations, an initial biopsy followed by elective surgery after 2–4 cycles of neoadjuvant chemotherapy can be considered.

5.2 Surgical Management of Mediastinal Tumors

Large mediastinal masses with a precarious airway must undergo surgical resection only after a proper risk assessment for anesthesia [26]. In a German cohort of 23 children with mediastinal GCTs, delayed resection was reported to increase the odds of complete resection of primary tumor with superior outcomes (EFS: 94% vs. 42%); an observation which was noted with SCTs as well [32]. Hence, in a secretory GCT, it would be well-judged to attempt a delayed resection following neoadjuvant chemotherapy. Approaches via lateral thoracotomy or median sternotomy are acceptable, and should include adherent non vital structures such as the thymus and pericardium with evaluation of regional lymph nodes when possible [11].

5.3 Chemotherapeutic Approaches

5.3.1 Clinicolaboratory Work-Up (Summarized in Table 4)

Chemotherapy

Platinum-based therapies have been the backbone of chemotherapy regimens for GCTs after a seminal study incorporating vinblastine, cisplatin and bleomycin [33]. Patients on this study had a survival rate of 64% and overall response rate of 100%. The present-day combination chemotherapy of bleomycin, etoposide and cisplatin (BEP) was the result of a randomized controlled trial with BEP arm having a better response rate in those with high tumor volume with fewer toxicities (neuromuscular) as compared to the vinblastine arm [34].

Table 4 Prechemotherapy evaluation and monitoring posttreatment

Prechemotherapy evaluation:

- Hemogram, renal function tests, liver function tests prior to every cycle of therapy
- Serial monitoring of tumor markers prior to every cycle
- Baseline measurements of glomerular filtration rate (GFR), pulmonary function tests (PFTs + DL-CO) and audiometry, which need to be reassessed mid-and end of-chemotherapy
- Although not standard in pediatric patients, oocyte preservation and sperm cryopreservation can be offered to postpubertal patients because of a small risk of infertility
- Clinical and radiological assessment should be performed after 2–4 cycles of chemotherapy

Surveillance postcompletion of therapy:

- Clinical evaluation at every follow-up visit
- Tumor markers (at the author's institution, tumor marker of interest is done at 3 monthly intervals for the first 12 months, 6 monthly intervals during the second year and yearly thereafter)
- Imaging of the primary tumor site is generally done if the tumor markers are elevated. In cases of teratomas however, serial ultrasound abdomen (in case of pelvic or abdominal tumors) or chest radiographs (in mediastinal primary) can be done.
- Serum electrolytes at every follow-up visit to look for tubular dysfunction.

Audiometry for only in symptomatic patients

Chemotherapy for pediatric GCT was adapted from these regimens by North American groups in their studies POG-9048 (low stage gonadal tumors) and POG-9049 (high-risk protocol) [35, 36]. Owing to concerns with bleomycin-related long-term pulmonary toxicity, the dose of bleomycin was reduced from 3 doses/cycle to 1 dose/cycle on day -1 alone, and termed PEb. PEb comprises Bleomycin 15 U/m^2 intravenous (IV) on day 1, Etoposide 100 mg/m^2/day IV on days 1–5 and Cisplatin 20 mg/m^2/day IV on days 1–5. Stage I gonadal tumors in boys were managed with surgical resection alone, and chemotherapy was given to other low stage gonadal (comprising of relapsed Stage I testicular tumors and Stage I/II ovarian tumors) tumors, yielding survival rates of 95% to 100% in this group of tumors. A randomized trial to assess the efficacy of high-dose cisplatin (HDPEB—200 mg/m^2/cycle) compared to standard-dose cisplatin (PEB—100 mg/m^2) in high-risk GCTs did not show a significant difference in 6-year OS between HDPEB and PEB (92% vs. 86%), although there was evidence of an increase in 6-year EFS among patients receiving HDPEB (89.6% ± 3.6% vs. 80.5 ± 4.8%, $p = 0.03$). Toxicity was much higher in the HDPEB arm with 6/7 (86%) of all deaths in HD PEB arm and 67% children requiring assisted hearing devices, thus limiting the use of this regimen.

Subsequent COG studies adopted a watch-and-wait policy for low-risk patients, reserving chemotherapy for those who

Table 5 Summary of treatment (chemotherapy) and outcomes of GCTs in the United States and United Kingdom [29, 39]

	United States (POG 9048, 9049, AGCT0132)			United Kingdom (GC – II)		
	Therapy	Number	6-year EFS/OS	Therapy	Number	4-year EFS/OS
Testicular						
Stage I	Observation	63	78.5%/100%	Observation	51[a]	78%/100%
Stage II–IV	4 PEb vs. HDPEb	60 (30/30)	89.8%/93.3%	JEb[b]	12	n = 137 87.8%/90.9%
Ovarian						
Stage I	Observation	25	52%/96% (*4 years*)	JEb[b]	54[c]	
Stage II–IV	4 PEb vs. HDPEb	74 (37/37)	94.5%/97.3%			
Extragonadal						
Stage I–IV	4 PEb vs. HDPEb	165 (82/83)	79.0%/83.4%	JEb[b]	67[d]	

[a] 11 children who relapsed on observation were given JEb chemotherapy

[b] Chemotherapy was given until remission plus 2 more

[c] 6 children were treated with surgery alone

[d] 1 child with thoracic stage I was treated with surgery alone

fail observation after surgery and assessed efficacy of 3 courses of PEb in a dose-intense fashion for intermediate-risk tumors. Among the stage I ovarian tumors, 52% were treated with surgery alone and 11/12 patients who had a relapse were successfully salvaged with an OS of 96%. Testicular stage I tumors had an excellent OS of 100% [37, 38]. Decrease in number of courses of PEb in intermediate-risk tumors led to an EFS of 89% but was less than an expected EFS of 92%, hence 4 cycles continue to remain the present standard treatment regimen for intermediate-risk patients.

GCT trials (GC-I, GC-II) in the United Kingdom utilized a carboplatin-based chemotherapy backbone (JEb) [38, 39]. JEb consists of carboplatin on day 2 in at an area under the curve (AUC) of 7.9 (AUC formula: [6 × *uncorrected GFR*] + [15 × *surface area*]), equivalent to approximately 600 mg/m^2; etoposide 120 mg/m^2/day for days 1 through 3 (total dose 360 mg/m^2); and bleomycin 15 mg/m^2 on day 3. Notably, in the GCI–GCII trials, the dose of carboplatin was more dose-intense and of higher dose as compared to contemporary protocols, and EFS and OS were comparable to that of COG studies which used cisplatin (Table 5), making carboplatin (at optimal dose intensity and frequency) a reasonable alternative to cisplatin due to ease of administration and favorable toxicity profile. The inferior outcomes that have been shown in adult GCT on carboplatin-based therapies are due to suboptimal dosing (AUC 3–5 versus AUC 7.9 or 350–500 mg/m^2), inadequate dose-intensity and a lower dose of other chemotherapy agents [40]. Data on head-to-head comparison of the efficacy and toxicity spectrum of cisplatin versus carboplatin in a randomized fashion at present is lacking [41]. A report of MaGIC consortium comparing the outcomes on GCTs treated on cisplatin or carboplatin by the COG and UKCCLG group found no significant difference in outcome observed overall or any subset of patients. Hence, there is parity in outcomes of pediatric GCTs treated with either cisplatin or carboplatin and little evidence to support choosing one over the other. For the final verdict, an international multicenter randomized controlled trial of carboplatin versus cisplatin, using pediatric carboplatin dosing and schedule, is underway [40]. Closer home, the outcomes are fairly comparable with a 5-yr-EFS/OS being between 60-70% and 70-80% respectively. Gonadal GCTs and low-interemdiate risk GCTs are associated with a better outcome. Regional challenges like late presentation, lack of AFP estimation prior to starting treatment, improper surgical techniques in the community (leading to stage migration and more intensive treatment), higher incidence of sepsis related deaths and treatment abandonment are hindrances to a better outcome [42–44].

Bleomycin in Pediatric GCTs

Bleomycin is an antitumor peptide which exerts its action by oxidative cleavage of DNA. Due to the serious (and often life-threatening) pulmonary toxicities of bleomycin, studies have focused on decreasing the cumulative doses of bleomycin. Adult and pediatric studies showed that reduction of therapy to two drugs (cisplatin + etoposide) and omitting bleomycin did not compromise outcome in selected cases [45, 46]. On German studies (MAKEI 83/86/89), following 2 deaths in children due to pulmonary fibrosis, bleomycin was entirely omitted from their subsequent protocol MAKEI/96 [47]. Most of the pediatric trials now use only a single dose of bleomycin (PEb/JEb) per cycle in their protocols. However, the current treatment algorithm in postpubertal GCT patients with poor risk (Table 4) recommends use of weekly bleomycin (i.e., 3 doses/cycle) [25].

5.4 Radiation Therapy

Indications of radiation therapy (RT) as a modality in upfront therapy of pediatric extracranial GCTs are fairly limited. In recurrent GCTs, radiotherapy is used when two lines of therapy are exhausted. German studies have reported the role of local RT to SCTs in unresectable cases; 3/5 patients who received RT >45 Gy were in continuous remission [48].

6 Toxicities of Treatment

Principal toxicities while on treatment are related to the chemotherapeutic agents in use and include myelotoxicity, ototoxicity, nephrotoxicity and pulmonary toxicity. The incidence of myelotoxicity is more with carboplatin-based regimens with major modification needed only in a small number of patients [49]. Otherwise, the incidence of ototoxicity is far less when compared to cisplatin-based chemotherapy.

To monitor these toxicities, baseline measurements of glomerular filtration rate (GFR), pulmonary function tests and audiometry, which need to be reassessed mid-and end of-chemotherapy. Although not standard in pediatric patients, oocyte preservation and sperm cryopreservation can be offered to postpubertal patients because of a small risk of infertility [11].

Details of late toxicities are outlined below in the section on late effects.

7 Late Effects

Survivors of childhood GCTs can potentially have 70 or more years of remaining life [41]. Therefore, identifying and tackling late effects assume importance. Because GCTs were not included in the Childhood Cancer Survivor Study, there is limited data on short-term and long-term data [50]. The St. Jude's database, a single-center experience with long-term effects in 73 survivors reports that nearly 50 (68%) had at least one long-term complication [51]. Several caveats like use of radiotherapy in frontline therapy and dose-intensive protocols incorporating alkylating agents (which are now archaic) in the above cohort restrict its wider extrapolation.

Toxicities of importance are outlined below:

- Ototoxicity: 60% of children treated with cisplatin develop permanent bilateral hearing loss. Platinum ototoxicity initially affects high-frequency hearing. High-frequency hearing loss causes difficulty in distinguishing high-frequency consonants that are critical for speech intelligibility, and it significantly impairs recognition of speech in the presence of background noise [52]. Although cisplatin is more ototoxic than other platinum-based drugs, carboplatin is also ototoxic, especially when delivered at myeloablative doses for autologous bone marrow transplantation or when administered in conjunction with osmotic opening of the blood–brain barrier [53]. A Phase-3 randomized trial on sodium thiosulfate (STS; an otoprotectant) in a heterogeneous population of children with solid tumors (16 GCTs in each arm) has demonstrated its efficacy, which needs to be validated in a larger cohort [54].
- Nephrotoxicity: Being a heavy metal, cisplatin remains in the body system for nearly 10 years after treatment. While glomerular function returns to 85% of pretreatment value within 4 years, the tubular function can stay impaired and persistent proximal tubular hypofunction has been reported in 20% patients [55].
- Pulmonary: The most serious complications of bleomycin are pneumonitis (bleomycin-induced pneumonitis–BIP) and pulmonary fibrosis which are estimated to be around 10% (adult studies) and can be life-threatening in up to 20% [56].
- Second malignancy: Adult studies have observed increased risk of secondary cancer occurring at 1% per year, with no plateau. Secondary leukemia after treatment with a conventional dose of etoposide does occur, but the low incidence does not alter the risk-to-benefit ratio of etoposide-based chemotherapy in germ-cell cancer [57].

8 Management of Recurrent/Relapsed Disease

Treatment options for recurrent pediatric GCTs are modeled on treatment options in adult clinical trials.

8.1 Surgery

Surgical resection in locally relapsed GCTs is still possible and patients achieve and sustain a durable remission if consolidated with salvage chemotherapy.

8.2 Chemotherapy

Limited data exist on optimal therapy for relapsed/refractory GCT. High-dose (HD) chemotherapy with autologous stem cell rescue has been explored as a treatment for adults with recurrent testicular GCTs. Pediatric data on HD chemotherapy is available only in small studies [58, 59]. Also, an appreciable percentage of patients fail to mobilize adequate hematopoietic stem cells (HSCs) numbers with granulocyte colony-stimulating factor (G-CSF) ± salvage chemotherapy, and require plerixafor for augmenting mobilization [60]. Experience from the author's centre (MP) on relapsed/refractory GCTs treated on conventional 2nd line chemotherapy regimens without autologous stem cell rescue showed that a small minority of patients with local relapses, gonadal primaries at baseline and with good biochemical response to 2 cycles (normalisation of tumor marker levels) could be salvaged with chemotherapy alone [61].

AGCT 0521 (COG Study) has used a combination chemotherapy of paclitaxel, ifosfamide and carboplatin (TIC) with a response rate of 44% (RECIST criteria and tumor marker decline) [62]. While TIC regimen can be considered as salvage in younger children (carboplatin instead of cisplatin) conventional dose chemotherapy with paclitaxel, ifosfamide and cisplatin (TIP) or HD chemotherapy with PI-CE (paclitaxel–ifosfamide followed by high-dose carboplatin–etoposide) are currently accepted standard options especially in adolescents. The AO31102 Alliance study (the TIGER trial; NCT02375204) will compare the survival of male patients randomized to conventional chemotherapy (TIP) versus PI-CE with stem-cell rescue [63].

9 Recent Advances

9.1 Role of miRNAs

As conventional tumor markers like AFP/beta-HCG are limited to specific tumor-subtypes within the larger cohort of malignant GCT, circulating miRNA have emerged as the next-generation tumor markers, with implications on treatment response and early detection of relapse [24].

9.2 Targeted Therapy

Because the pathogenesis of adult GCTs differ from pediatric GCTs, identifying and targeting the putative pathways for pediatric GCTs, viz., Wnt/β-catenin, BMP, notch and hedgehog should be the way forward.

10 How We Do It at TMC

Baseline Work-up

- **Diagnostic Investigations:** Serum alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-CG).
- **Imaging:** CT/MRI of the primary site.
- **Pathology:** Biopsy is not mandatory except when the tumor markers are normal and/or clinicoradiological noncorrelation.
- **Staging:** CT chest/abdomen.

Staging

The TMC uses a risk-stratified approach as outlined in Table 6.

Chemotherapy Regimen

- Cisplatin: 33.3 mg/m^2/dose D1–D3.
- Etoposide: 167 mg/m^2/dose D1–D3.
- Bleomycin: 15 units/m^2/dose D1 only.
- Four cycles for intermediate/high-risk GCTs.
- No chemotherapy for low-risk GCTs.

Pediatric GCTs in TMC are managed as per an algorithmic approach (Fig. 2) [64].

Table 6 Risk-stratified therapy

Risk category	Stage/Site	Treatment
Low risk	Stage I testes, stage I ovary	Surgery alone and observe
Intermediate risk	Stage II–IV testes Stage II–III ovary Stage I–II extragonadal	Surgery and chemotherapy (4 cycles)
High risk	Stage IV ovary Stage III–IV Extragonadal	Surgery and chemotherapy (6 cycles)

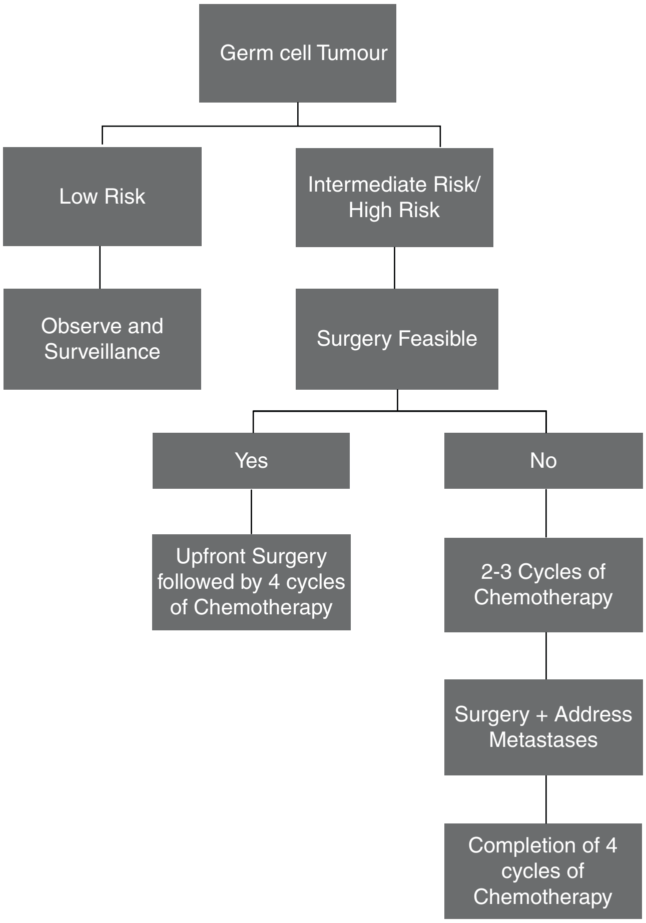
Germ cell Tumour
Low Risk
Intermediate Risk/ High Risk
Observe and Surveillance
Surgery Feasible
Yes
No
Upfront Surgery followed by 4 cycles of Chemotherapy
2-3 Cycles of Chemotherapy
Surgery + Address Metastases
Completion of 4 cycles of Chemotherapy

Fig. 2 Tata Memorial Centre algorithmic approach to management [63]

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Hepatoblastoma

Maya Prasad

Abbreviations

AFP	Alpha-fetoprotein
CECT	Contrast-enhanced abdominal computerized tomography
HACE	Hepatic artery chemoembolization
HB	Hepatoblastoma
HCC	Hepatocellular carcinoma
hCG	Human chorionic gonadotropin
hFLMPC	Human fetal liver multipotent progenitor cell
MRI	Magnetic resonance imaging
OLT	Orthotropic liver transplantation
SCU	Small cell undifferentiated
TACE	Transarterial chemoembolization

1 Introduction

Hepatoblastoma (HB) is the most common primary malignant liver neoplasm in children and is predominantly a tumor of infants and young children. Even so, it comprises only 1% of all pediatric malignancies [1]. Advances in multidisciplinary care, including those in imaging, chemotherapy, surgery and increasing use of liver transplantation, have led to improved outcomes in hepatoblastoma over the past few decades from 20% to 80%. These in turn have been spearheaded by collaborative groups across the globe, mainly Children's Oncology Group (COG), Liver Tumour Group of International Society of Pediatric Oncology (SIOPEL), the Japanese Pediatric Liver Tumor Group (JPLT) and German Pediatric Hematology Oncology Group (GPOH) [1].

2 Incidence and Epidemiology in India and Globally

The annual incidence of HB in the United States was reported to be 1.6 cases per 1 million children aged 18 years and less during 2002–2009 [2].

Although the exact incidence of HB in India is not known, hospital-based registries have reported hepatic tumors to be 0.5% to 4.5% of all childhood tumors in children less than 14 years [3].

Although most cases of HB are sporadic, there is a known association with constitutional genetic abnormalities such as Beckwith–Wiedemann syndrome familial adenomatous polyposis and trisomy 18 [4]. Hepatoblastoma is strongly associated with very low birth weight (VLBW; <1500 g), with odds ratio ranging from 9.5 to 69. The exact reason for this association is not known; gestational age does not appear to be a factor [4].

3 Clinical Presentation in India and Globally

HB is a tumor of very young children, and nearly all develop the tumor before 3 years of age; HB accounts for 90% of malignant liver tumors in children aged 4 years and younger [5]. Literature from India reports a median age at presentation of 7 to 34 months and a variable, but mostly higher incidence of pretext III and IV lesions. Outcomes are also variable, but mostly lower (5-year event-free survival of 67–80%) than in Western literature [6–12].

The common presentations are abdominal distension or abdominal mass, which could cause respiratory distress, discomfort and fatigue and loss of appetite. Less common presentations include tumor rupture and precocious puberty/virilization in tumors which secrete β-human chorionic gonadotropin (hCG).

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4 Evaluation and Work-Up

4.1 Tumor Markers

Serum alpha-fetoprotein (AFP) is elevated in 90% of cases of hepatoblastoma, and S.AFP levels are important in diagnosis, prognosis and response to treatment. Variants such as small cell undifferentiated (SCU) hepatoblastoma are associated with low levels of S. AFP and dismal prognosis [13]. S. AFP levels are very high during the neonatal period and decrease consistently during the first year of life, reaching near-normal levels by 6 months of age (Table 1) [14]. The half-life of AFP is 5 to 7 days.

4.2 Radiology

Radiology is important in diagnosis, risk stratification and response assessment in hepatoblastoma. Although ultrasound of the liver is often the initial imaging procedure, the gold standard for diagnosis of hepatoblastoma is either a triphasic (noncontrast, arterial and venous phases) contrast-enhanced abdominal computerized tomography scan (CECT) or magnetic resonance imaging (MRI) with contrast agents such as gadoxetate disodium. Hepatoblastoma shows up on CT scans as a well-defined heterogeneous mass with lower attenuation compared to the normal liver. Areas of necrosis and hemorrhage as well as calcification may be seen. MRI is superior to CT in defining tumor margins, vessel involvement and adenopathy [15].

The extent of liver involvement and operability of tumor are defined using the Pre-Treatment Extent of Tumor or PRETEXT system [16–18]. The liver is divided into four parts called sectors, with the left lobe of the liver consisting of medial (Couinaud segment 4) and lateral sectors (segments 2 and 3) and right lobe consisting of anterior (segments 5 and 8) and posterior sectors (segments 6 and 7). Since Couinaud segment one corresponds with the caudate lobe, it is not included in this division. PRETEXT categories depend on the number of liver sectors free of tumor and describe the extent of tumor within the liver, while other factors such as venous or extrahepatic involvement or metastatic disease are denoted by "annotation factors" (Fig. 1) (Table 2). The PRETEXT system takes into account imaging features prior to start of treatment and has prognostic implications. PRETEXT was originally described by the Epithelial Liver Tumour group of Société Internationale d'Oncologie Pédiatrique (SIOPEL) in order to standardize imaging and risk stratification for its first study SIOPEL-1; it has subsequently been adopted by other major collaborative groups which conducted studies in hepatoblastoma such as the North American Children's Oncology Group (COG) and Japanese Study Group for Pediatric Liver Tumor (JPLT) [18]. PRETEXT classification following chemotherapy is denoted as POSTTEXT.

Table 1 Normal range of serum AFP values in normal-term babies[a]

Age (in Days)	Mean AFP (ng/mL)	AFP 95% Range (ng/mL)
0	41,687	9120–190,546
1	36,391	7943–165,959
2	31,769	6950–144,544
3	27,733	6026–125,893
4	24,210	5297–109,648
5	21,135	4624–96,605
6	18,450	4037–84,334
7	16,107	3524–73,621
8–14	9333	1480–58,887
15–21	3631	575–22,910
22–28	1396	316–6310
29–45	417	30–5754
46–60	178	16–1995
61–90	80	6–1045
91–120	36	3–417
121–150	20	2–216
151–180	13	1.25–129
181–720	8	0.8–87

[a] Adapted from [14]

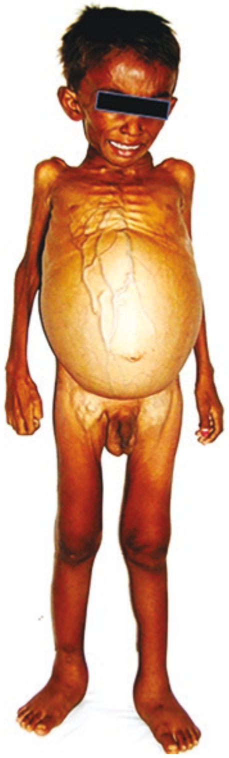

Fig. 1 PRETEXT Staging system. Reprinted with permission from Roebuck DJ, Aronson D, Clapuyt P, Czauderna P, de Goyet JD, Gauthier F, et al. 2005 PRETEXT: a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. Pediatr Radiol 2007 Feb 1;37(2):123–32

Table 2 PRETEXT Staging system [16]

Pretext group	Description
I	One section involved; three adjoining sections are tumor free
II	One or two sections involved; two adjoining sections are tumor free
III	Two or three sections involved; one adjoining section is tumor free
IV	Four sections involved
Annotation factors	
V	Venous involvement: Vascular involvement of the retrohepatic vena Cava or involvement of all three major hepatic veins (right, middle and left)
P	Portal involvement: Vascular involvement of the main portal vein and/or **both** right and left portal veins
E	Extrahepatic involvement of a contiguous structure such as the diaphragm, abdominal wall, stomach, colon, etc.
M	Distant metastatic disease (usually lungs, occasionally bone or brain)
R	Tumor rupture
N	Lymph node involvement
F	Multifocality
C	Caudate lobe involvement

4.3 Pathology

A biopsy may not be required in children aged 6 months to 3 years with clinical and radiological features typical of hepatoblastoma and raised serum AFP levels, or when radiological features are typical of infantile hemangioma or focal nodular hyperplasia.

Hepatoblastoma arises from precursors of hepatocytes B and also from less differentiated cells such as hepatic stem cells and human fetal liver multipotent progenitor cells (hFLMPCs). Morphology is most often a mixture of epithelial hepatocyte precursors, but can be heterogeneous. The most recent classification of hepatoblastoma has two groups—epithelial tumors (which includes fetal, embryonal, macrotrabecular, small-cell undifferentiated and cholangioblastic) and mixed tumors (stromal derivatives or teratoid) [19]. Tumors with well-differentiated "pure fetal" histology have an excellent prognosis, and completely resected tumors may not require adjuvant chemotherapy [20]. Tumors with small cell undifferentiated histology are seen in infants, present with low or normal levels of serum AFP (<100 ng/dL) and have features overlapping with rhabdoid tumor of liver, including dismal prognosis. The presence of even small foci of this histology warrants aggressive chemotherapy [21].

5 Principles of Management of Hepatoblastoma

There been tremendous improvement in the survival of children with hepatoblastoma from 20% to 80% over the past few decades [1]. This progress can be attributed to better understanding of surgical anatomy of liver, improved risk stratification, effective neoadjuvant chemotherapeutic agents and the availability of liver transplantation. These improvements have been largely due to multiple clinical trials by cooperative groups across the globe, which have adopted different treatment approaches but with similar outcomes. The European SIOPEL group advocates neoadjuvant chemotherapy followed by surgery in order to decrease tumor size and vascularity, improve resectability and address micrometastasis [1, 22]. In contrast, the North American COG recommends upfront surgery wherever possible, followed by chemotherapy. However, the PRETEXT classification as well as similar chemotherapy agents are common to both groups (as well as German Pediatric Hematology Oncology Group, GPOH and Japanese Pediatric Liver Tumor group, JPLT). These differing approaches have not been compared in a controlled manner. Recently, the Children's Hepatic Tumors International Collaboration (CHIC) merged data from eight collaborative hepatoblastoma trials to form a database of 1605 patients, which was then used to develop a global uniform risk stratification system, in turn laying the framework for the prospective international such as Paediatric Hepatic International Tumour Trial (PHITT) [23].

The SIOPEL group was formed in 1987 as an international (but Eurocentric) collaborative group of pediatric surgeons, oncologists, pathologists and radiologists who would focus on childhood liver tumors. There have been six trials conducted by this group which included patients with both hepatoblastoma (HB) and hepatocellular carcinoma (HCC) (Table 3).

Table 3 Summary of collaborative studies in hepatoblastoma

Study	Era and patients	Key messages
SIOP studies		
SIOPEL 1 [24–27]	1990–1994 153 HB; 40 HCC	PRETEXT staging Neoadjuvant chemotherapy (cisplatin–doxorubicin) followed by delayed surgery as standard of care Liver transplantation could increase resection rate
SIOPEL 2 [28]	1994–1998 135 HB; 20 HCC *pilot study of risk-stratified approach	Introduction of risk categories based on SIOPEL 1 results: Standard risk (SR) and high risk (HR) Risk-stratified treatment: Standard risk—cisplatin alone High risk—combination of cisplatin/doxorubin/carboplatin (Super PLADO) Efficacious in SR HB and acceptable toxicity in SR/HR
SIOPEL 3 [29, 30]	SIOPEL 3 SR-HB (1998–2005)—Prospective randomized trial on SR HB SIOPEL 3 HR-HB (1998–2004)—Prospective single-arm trial on HR HB 406 HB; 65 HCC	Standard risk—cisplatin alone as effective as PLADO and less toxic; High risk—combination of cisplatin/doxorubin/carboplatin (Super PLADO) significantly better than PLADO(cisplatin/ doxorubicin) Liver transplantation encouraged
SIOPEL 4 [31]	2005–2009 Prospective single-arm feasibility 62 HB	Intensified treatment of HR HB Neoadjuvant chemotherapy with weekly cisplatin, monthly doxorubicin followed by delayed surgery (carboplatin-doxorubicin, in those with poor response to NACT) Improved outcomes compared to historical controls
SIOPEL 5	2005–2009 Closed due to insufficient recruitment	Prospective single-arm trial devoted exclusively to the HCC
SIOPEL 6 [32]	2007–2017	Randomized controlled trial of cisplatin monotherapy with/without sodium thiosulfate Primary endpoint: To see if coadministration of sodium thiosulfate decreases hearing loss Interim analysis encouraging
SIOPEL RCN [33]		Risk-stratified treatment for resource-challenged nations (RCN) based on SIOPEL 3 study: SR—cisplatin monotherapy HR—1 cycle cisplatin and 5 cycles of PLADO
North American studies		
INT0098 [34]	1989–1992	No statistically significant differences in survival between cisplatin + fluorouracil + vincristine (C5V) or cisplatin + doxorubicin (PLADO) Cisplatin is the most active agent against HB
P9645 [35]	1999–2002 108 HB	Intensification of therapy by alternating cisplatin/carboplatin increased the risk of adverse outcome in unresectable/metastatic HB
COG AHEP 0731 [36]	Ongoing	Very-low-risk group: Surgery followed by observation Low-risk group: Surgery followed by C5V chemotherapy (cisplatin, fluorouracil, vincristine) Intermediate-risk group (regimen F): C5VD chemotherapy (cisplatin, fluorouracil, vincristine doxorubicin) High-risk group (regimen H): Upfront VIT chemotherapy (vincristine, irinotecan, temsirolimus) followed by C5VD chemotherapy alternating with VIT
German (GPOH) studies		
HB 89 [37]	1988–1992 37 HB	Advanced/metastatic HB Complete resection is essential for survival from advanced hepatoblastoma to prevent drug resistance Initial S.AFP values <100 ng/mL or > 1,000,000 ng/mL, slow decline of AFP, growth pattern of tumor within the liver (and vascular tumor invasion prognostic factors
HB 99 [38]	1999–2004 45 HB	Use of high-dose chemotherapy (CARBO/VP16) in HR HB
Japanese Paediatric Liver Tumour Group (JPLT) studies		
JPLT-1 [39]	1991–1999 145 HB	Stage I /II HB—cisplatin, pirarubicin (tetrahydropyranyl-adriamycin) low dose Stage IIIA, IIIB, IV HB: CDDP, pirarubicin higher dose Poor outcome for advanced HB
JPLT-2 [40]	1999–2010 212 HB	PRETEXT I: Primary resection followed by low doses of cisplatin-pirarubicin Others: Preoperative cisplatin-pirarubicin (CITA), followed by surgery and postoperative chemotherapy Salvage: Ifosfamide, pirarubicin, etoposide and carboplatin (ITEC) Metastatic diseases: High-dose chemotherapy with hematopoietic stem cell transplantation (SCT) Improved outcomes

6 Risk Stratification and Prognostic Factors

As with most other pediatric tumors, the treatment of hepatoblastoma is tailored to risk. Risk categories have been variously defined by major collaborative groups (see Table 4). Chemotherapy recommendations as per risk category are in Table 5.

Table 4 Risk stratification of hepatoblastoma [28]

	Very low risk	Standard/low risk	High risk
SIOPEL:		PRETEXT I, II or III	Any PRETEXT; V+, P+, E+, M+; SCU histology; AFP level < 100 ng/mL; tumor rupture
COG	PRETEXT I or II; well-differentiated fetal histology; primary resection at diagnosis	PRETEXT I or II of any histology with primary resection at diagnosis	Any PRETEXT with M+; AFP level < 100 ng/mL
Intermediate risk as per COG—PRETEXT II, III or IV unresectable at diagnosis; or V + C+, P+, E+; SCU histology small cell undifferentiated histology			

Table 5 Current recommendations for risk-stratified chemotherapy in hepatoblastoma [22, 28–30, 36, 38, 39]

Study group	Risk group	Neoadjuvant chemotherapy	Adjuvant chemotherapy
COG	Very low risk	NIL	NIL
	Low risk	NIL	C5V × 2
	Intermediate risk	C5V-DOXO × 4–6	C5V-DOXO × 2
	High risk	VCR-IRINO × 2 + C5V-DOXO × 6	
SIOPEL	Standard risk	CDDP × 4	CDDP × 2
	High risk	CDDP × 4 alternating with carbo/Doxo × 3	CDDP × 1 alternating with carbo/Doxo × 2
GPOH	Standard risk	PLADO × 2–3 or IPA	PLADO × 1
	High risk	CDDP × 4 alternating with carbo/Doxo × 3 or carbo/etoposide	CDDP × 1 alternating with carbo/Doxo × 2
JPLT	PRETEXT I	–	CITA × 4 (50% DOSE)
	PRETEXT II	CITA × 2	CITA × 4 (50% DOSE)
	PRETEXT III/ IV or EVPH+ M+	CITA × 4 CITA × 4+ high dose etoposide/carbo/Melphalan ± HACE	CITA × 2 CITA × 2

C5V cisplatin +5-fluorouracil + vincristine, *CDDP* cisplatin, *carbo* carboplatin, *Doxo* doxorubicin, *PLADO* cisplatin + doxorubicin; *CITA* cisplatin + pirarubicin, *EVPHM* extrahepatic/venous involvement/portal vein invasion/tumor rupture/metastasis, *IPA* ifosfamide/cisplatin/doxorubicin, *HACE* hepatic artery chemoembolization, *COG* Children's oncology group, *SIOPEL* International Society of Pediatric Oncology-Liver Tumour Strategy Group, *GPOH* German Pediatric Hematology Group, *JPLT* Japanese Pediatric Liver Tumor Study Group, *VCR* vincristine; Irino, irinotecan

7 Surgical Management

Surgery is a key component in management of hepatoblastoma, and complete resection is essential to improve outcome. However, over 50% of HB are unresectable at diagnosis [34]. SIOPEL recommends complete surgical resection of primary tumor as well as metastatic sites, the timing of surgery being generally after four or seven cycles of neoadjuvant chemotherapy. Delaying surgery further has not been found beneficial [41]. The current COG protocol AHEP0731 recommends upfront surgical resection (lobectomy or segmentectomy) in PRETEXT I tumors and selected PRETEXT II tumors which are completely resectable. POSTTEXT II and III without macroscopic venous involvement are recommended to undergo neoadjuvant chemotherapy followed by lobectomy or trisegmentectomy. POSTTEXT III tumors with macroscopic venous involvement or POSTTEXT IV tumors would require neoadjuvant chemotherapy followed by re-evaluation for surgery—these tumors might require extreme/complex resection or even orthotropic liver transplantation. Incomplete resection and macroscopic residual disease confer a worse outcome, and if these are anticipated, orthotropic liver transplantation (OLT) should be performed [36]. Successive trials optimizing chemotherapy have increased the resectability of tumors (see Table 3). Atypical, nonanatomic or wedge resections are associated with inferior outcomes and thus not recommended.

7.1 Surgery for Lung Metastases

Lung metastases often respond well to neoadjuvant chemotherapy and may completely disappear. Residual metastatic disease needs to be surgically removed. Wedge resection is a preferred technique for the removal of pulmonary deposits.

7.2 Role of Orthotropic Liver Transplantation [42]

The advent and increasing use of OLT have enabled increased resection in hepatoblastoma. Although OLT necessitates infrastructure, resources and long-term immunosuppression in small children, it is preferred over risky surgery in certain subsets of patients. Indications for OLT include:

- Multifocal HB in all four liver sections (PRETEXT IV)
- Solitary PRETEXT IV HB that are not clearly downstaged to POSTTEXT III
- Portal vein involvement
- Involvement of all three hepatic veins (V3)
- Central HB (if a conventional resection does not seem feasible

The current COG study (AHEP0731) advocates early referral for OLT, i.e., based on imaging done **after** the second cycle of chemotherapy. Posttransplantation chemotherapy has been observed to improve survival and hence should be administered even at the cost of increased toxicity.

The Pediatric Liver Unresectable Tumor Observatory (PLUTO) is an online registry which collects information on unresectable HB, mostly those undergoing OLT.

8 Medical Management

Hepatoblastoma is a chemosensitive tumor. The current chemotherapeutic strategies in hepatoblastoma are a result of multiple collaborative studies, mainly by SIOPEL and COG (see Table 3). Optimization of chemotherapy has been a key reason for improved outcomes in HB, especially since over half tumors are unresectable at diagnosis. The earlier trials recognized cisplatin to be the most effective chemotherapeutic agent in HB, and it is the backbone of all chemotherapeutic regimens.

Neoadjuvant chemotherapy has been found to reduce tumor size and volume, decrease vascularity and demarcate it from normal liver tissue, thus increasing resectability. It may also lead to the complete disappearance of macroscopic lung metastases and act on microscopic metastasis. These are the rationale behind the SIOPEL approach of neoadjuvant chemotherapy followed by delayed surgery. SIOPEL chemotherapy in standard-risk hepatoblastoma consists of four cycles of cisplatin monotherapy followed by surgery and two more cycles of cisplatin. SIOPEL chemotherapy in high-risk hepatoblastoma consists of ten cycles of alternating cisplatin and carboplatin/doxorubicin (SUPER PLADO); this strategy allows for a higher dose of platinum while decreasing the dose of toxic cisplatin (see Table 5). The North American (currently COG) groups prefer surgery wherever safely possible followed by adjuvant chemotherapy. Stage 1 tumors with pure fetal histology can be safely observed after complete resection [20]. The current COG trial, AHEP 0731 is testing the efficacy of further reduction in therapy [36]. There are four risk groups (see Table 5): “very low risk” patients are observed after surgery, and “low-risk” patients undergo surgery followed by two courses of adjuvant chemotherapy with cisplatin, fluorouracil IV and vincristine (regimen T). “Intermediate-risk” patients on AHEP0731 receive six courses of C5VD chemotherapy with cisplatin, fluorouracil, vincristine and doxorubicin (regimen F) with surgery (± liver transplantation) after two to four courses. “High-risk” patients receive two courses of upfront VIT chemotherapy with vincristine, irinotecan and temsirolimus followed by six courses of C5VD interspersed with VIT (regimen H) and surgery after course 4. No controlled comparison has been performed between the SIOPEL and

COG treatment strategies. However, the survival rates of patients treated with both approaches are comparable.

9 Other Modalities of Treatment

Tumors which are unresectable even after neoadjuvant chemotherapy may benefit from alternative approaches, the most promising of which is transarterial or hepatic artery chemoembolization (TACE/HACE), which has been used to improve resectability of HBs [43]. Intra-arterial chemotherapy with drugs such as cisplatin and doxorubicin is followed by embolization of the feeding arteries of the tumor.

Currently, there is no evidence for use of radiotherapy in hepatoblastoma unless in palliative setting.

10 Toxicity of Treatment in Hepatoblastoma

Hepatoblastoma is typically a disease of very young children, who are at risk for acute toxicities as well as late effects of treatment. The major toxicities include ototoxicity, renal tubular toxicity and cardiotoxicity. Understanding of these toxicities has led to increasing use of risk-stratified treatment to avoid unnecessary treatment exposures in a large proportion of children.

10.1 Ototoxicity

Hearing loss is often a permanent side effect of cisplatin chemotherapy; SIOPEL studies have shown that over 60% of children had permanent high-frequency hearing loss [44]. Since affected children are often very young, hearing loss can affect development of speech, learning and overall development. Age-appropriate monitoring of hearing needs to be done during, and after completion of treatment, with pure-tone audiometry being the standard in older children. Two large studies from COG and SIOPEL have found that sodium thiosulfate is safe and efficacious in reducing the incidence of cisplatin induced hearing loss, when given 6 h after cisplatin infusion. While the COG study ACCL0431 included multiple tumor diagnoses, SIOPEL-6 was restricted to children with standard-risk hepatoblastoma [32, 45].

10.2 Nephrotoxicity

Both glomerular and tubular toxicity are common with cisplatin. Judicious hydration and monitoring of renal function and electrolytes should be done during treatment and at follow-up.

10.3 Cardiotoxicity

High cumulative doses of doxorubicin place young children at high risk of acute and long-term cardiac toxicity. Periodic monitoring during and after treatment is essential. Current and upcoming trials such as AHEP 0731 and the PHITT trial recommend the use of cardioprotectant dexrazoxane.

11 Stage-Wise Prognosis with Current Treatment

Survival in standard-risk hepatoblastoma is uniformly good with 5-year event-free survival of 83% and overall survival of 95%, whereas 3-year event-free survival is 65% and 3-year overall survival is 69% in high-risk hepatoblastoma [29, 30]. Outcomes of hepatoblastoma in resource-limited settings are lower, mainly due to advanced presentations, treatment-related mortality, lack of appropriate risk stratification and paucity of centers with surgical expertise (including liver transplantation).

12 Management of Recurrent Disease Including Specific Palliative Measures

Recurrent hepatoblastoma is a challenge to treat. Prognosis depends on previous treatment, site of recurrence and extent of disease spread.

Second-line chemotherapy regimens would depend on initial treatment. Combination of vincristine-irinotecan and addition of doxorubicin have been tried with limited success. Aggressive and complete resection improves the outcome, and liver transplantation should be considered in difficult resections [46].

Summary

- Hepatoblastoma (HB) is the most common primary malignant liver neoplasm in children,
- Comprises only 1% of all pediatric malignancies.
- Diagnostic investigations include serum alpha-fetoprotein (AFP), which is elevated for age, and imaging, preferably triple-phase contrast-enhanced CT abdomen/MRI.
- The PRETEXT system is used to define the extent of liver involvement and determine operability, and has prognostic implications.
- Conventionally, hepatoblastoma is risk stratified into standard (good) risk and high risk, and current treatment is based on decades of collaborative efforts.
- Hepatoblastoma requires multidisciplinary management of which surgery is the mainstay.
- Young children need careful monitoring for the development of acute and late toxicities of treatment.

How We Do It at TMC (Fig. 2).

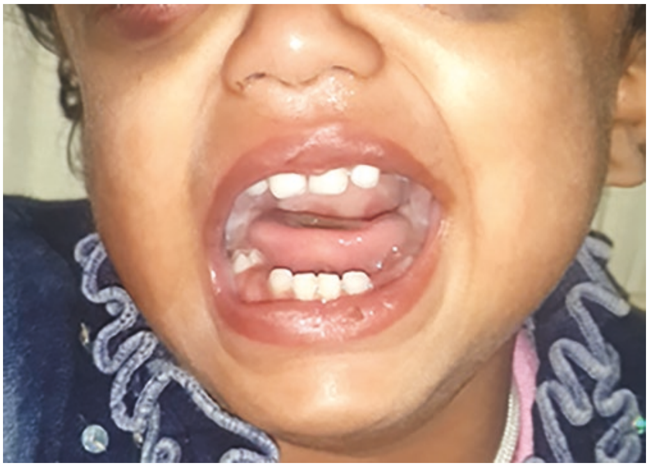

Fig. 2 TMH treatment algorithm for hepatoblastoma

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Part V

Special Topics in Oncology

Emergencies

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Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ARI	Acute renal injury
CTLS	Clinical TLS
LTLS	Laboratory TLS
NHL	Non-Hodgkin lymphoma
SVC	Superior vena cava
SVCO	SVC obstruction syndrome
TLS	Tumor lysis syndrome

1 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is an oncologic emergency resulting from rapid cell death. It can happen either spontaneously or after initiation of chemotherapy. Cairo and Bishop [1] defined TLS as either laboratory TLS (LTLS) or clinical TLS (CTLS). LTLS is defined as the occurrence of two or more of the following abnormalities, 3 days before or 7 days after initiation of chemotherapy: 1) 25% decrease from baseline in serum calcium and/or 2) 25% increase from baseline in the serum values of uric acid, potassium, or phosphorous. CTLS defined as presence of LTLS along with one or more clinical manifestations like cardiac arrhythmia, death, seizure, or acute renal injury (ARI) with an elevated serum creatinine >1.5 times upper limit of normal. Wilson and Berns [2] have modified definition of ARI, 0.3 mg/dL absolute increase, or relative 50% increase in creatinine over baseline.

1.1 Incidence and Risk Factors

TLS is more common in patients with tumors that have a large tumor mass and a high proliferation rate. Hematologic malignancies such as non-Hodgkin lymphoma (NHL), particularly Burkitt-type lymphoma, acute lymphocytic and lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), chronic leukemias, and multiple myeloma are associated with increased of TLS. Rarely, TLS can develop in solid malignancies like small-cell carcinoma of the lung, germ cell tumors, neuroblastoma, and breast carcinoma.

1.2 Pathophysiology

Rapid lysis of tumor cells either spontaneously or as a consequence of chemotherapy and releases intracellular contents like potassium, phosphorus, and nucleic acids. This causes a diversity of biochemical changes which leads to different clinical signs of TLS. Hyperkalemia can cause arrhythmias and sudden death. Hyperphosphatemia can cause formation of calcium phosphate complexes which crystallizes renal tubules, leading to ARI. The resulting hypocalcemia causes symptoms like tetany, seizures, and dysrhythmia.

Nucleic acids are metabolized to hypoxanthine, xanthine, and finally to uric acid by xanthine oxidase enzyme. Hyperuricemia can cause urate crystallization and precipitation in renal tubules leading to ARI. Increased serum uric acid levels can induce ARI by further mechanisms, like renal vasoconstriction, reduction in endothelial cell nitric oxide, and activation of the renin–angiotensin system [3]. Renal clearance of uric acid depends on glomerular filtration rate and urine pH (enhanced by urine alkalinization). Therefore,

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crystal-induced ARI can be caused by uric acid, calcium phosphate, and xanthine precipitation.

Patients are classified into three risk groups (high, intermediate, and low risk) as per patient-related factors (preexistent renal dysfunction and hyperuricemia) and tumor-related factors (tumor mass, type of tumor [indicated by stage of tumor, white blood cell counts, and LDH levels]) [4].

1.3 Prevention and Treatment

Since TLS is a life-threatening emergency, prevention of TLS is the key principle in its management. It is recommended to start with a low-dose therapy in highly chemosensitive tumors with high tumor burden. In patients, at intermediate and high risk for TLS, it is necessary to monitor serum electrolytes and renal function tests at least twice daily, before starting systemic therapy and during the first 7 days of treatment.

1.3.1 Hydration

Hydration should be done with normal saline at a rate of 3 L/m^2/24 h, especially in patients with intermediate and high risk for TLS. Close monitoring of fluid intake and output is required, and a urinary output 100 mL/h 24 h should be targeted. Hydration must begin before starting systemic therapy and through the duration of treatment (at least for first 7 days). Special care should be done for elderly patients and those with cardiac dysfunction. In case of low urine output even after an optimal hydration, loop diuretics can be given. Thiazide diuretics should be avoided as they interact with allopurinol and can increase uric acid levels.

1.3.2 Electrolyte Abnormalities

Asymptomatic hypocalcemia should not be treated as it can lead to calcium phosphate crystal precipitation in renal tubules. Symptomatic hypocalcemia should be treated with infusion of calcium gluconate [5]. Potassium should not be added to hydration fluid to avoid hyperkalemia. Patients with potassium levels >6 mmol/L should be carefully observed, and immediate treatment should be given (infusion of calcium gluconate, insulin and glucose infusion, and therapy with β-adrenergic agonists).

Oral phosphate binders like Sevelamer or antacids syrup can be used to treat hyperphosphatemia. These measures are usually less effective. Significant hyperphosphatemia is best treated with hemodialysis (renal replacement therapy).

1.3.3 Renal Replacement Therapy

Renal replacement therapy should be considered for patients with severe acidosis, persistent hyperkalemia inspite of adequate therapy, and volume overload despite diuretic therapy.

1.3.4 Alkalinization of Urine

Alkalinization of urine was historically recommended in the management of TLS as it may increase the solubility of uric acid in urine. However, recent evidence advocates that urine alkalinization increases the risk of calcium phosphate precipitation in the renal tubules, especially in patients with hyperphosphatemia. Hence, alkalinization of urine is not being recommended now in TLS prophylaxis [6].

1.3.5 Antihyperuricemic Therapy

Hyperuricemia plays a key role in evolving ARI [3]. The most commonly used antihyperuricemic agents are allopurinol (xanthine oxidase inhibitor) and rasburicase (recombinant urate oxidase).

Allopurinol

Allopurinol prevents the conversion of hypoxanthine to xanthine and xanthine to uric acid. Hypoxanthine and xanthine are cleared ten times faster than uric acid by renal tubules. Allopurinol requires dose adjustment in case of renal dysfunction. It should be started one day prior to initiation of anticancer therapy and be continued until normalization of uric acid levels. However, allopurinol cannot decrease the level of preexisting uric acid and can lead to increases in serum levels of xanthine and hypoxanthine, which can cause xanthine nephropathy [7]. Therefore, allopurinol can be used for patients at low or intermediate risk for TLS. In case of established TLS, rasburicase should be considered.

Febuxostat

Febuxostat is a selective xanthine oxidase inhibitor [8] and has biliary elimination [9]. In patients with renal dysfunction or with hypersensitivity to allopurinol, febuxostat is an alternative option.

Rasburicase

Rasburicase is a recombinant, urate oxidase enzyme that convert uric acid is to allantoin. Allantoin is ten times more soluble than uric acid and thus easily cleared through renal tubules [10].

The FDA-approved dose is 0.15–0.20 mg/kg/day as a single intravenous infusion for 5 days. Several trials compared a single dose of rasburicase with daily dosing for 5 days. The single dose of rasburicase was as efficient as the multiple day dosing regimen for majority of patients [11–15].

A meta-analysis [16] compared the efficacy of a single-fixed dose of rasburicase versus the dose for 5 days versus allopurinol in adult patients at high risk for TLS (10 studies). This analysis proved that a single-fixed dose of rasburicase is noninferior to 5 days regimen and rasburicase was superior to allopurinol. Rasburicase is contraindicated in patient with

G6PD deficiency as it can lead to methemoglobinemia in G6PD-deficient patients [17].

2 Conclusion

TLS is a life-threatening emergency that can occur either spontaneously or after anticancer therapy. Prevention is the most effective therapy. Recognition of patients at risk for TLS is crucial. The diagnostic criteria and classification proposed by Cairo and Bishop facilitate early risk stratification of patients. Hydration with close monitoring of intake and output balance and serum electrolytes levels is crucial.

2.1 Pediatric Emergencies

Children with cancer are at increased risk of life-threatening emergencies, either from the cancer or due to treatment of cancer [18]. These conditions need to be diagnosed and treated early to lessen morbidity and mortality. Pediatric emergencies are broadly divided into cardiothoracic and abdominal emergencies.

2.2 Cardiothoracic Emergencies

2.2.1 Superior Vena Cava Syndrome

Obstruction of the superior vena cava (SVC) causes venous congestion leading to a constellation of signs and symptoms called as SVC obstruction syndrome (SVCO) [19]. SVC obstruction can be caused either by extrinsic or intrinsic obstruction. An anterior mediastinal mass (by either lymphoma or leukemia]) is the most common cause of SVCO [2]. Other common malignancies that can cause SVCO are lung cancer, neuroblastoma, and germ-cell tumors [19]. Prolonged placement of central venous catheter is also a risk factor of acquiring SVC thrombosis [20]. The common symptoms are facial swelling, cough, dyspnea, orthopnea, and wheeze. Chest X ray shows mediastinal widening and airway compression due to mediastinal mass [20, 21]. Contrast-enhanced CT scan of chest shows tumor and its extension into surrounding vasculature and airway. Diagnosis of mediastinal mass leading to SVC syndrome should be made with the least invasive technique to avoid cardiorespiratory compromise [21, 22]. Peripheral blood analysis for surface markers studies, pleural fluid cytology and cell block preparation, bone marrow aspiration, or biopsy of the most easily accessible extra-thoracic lesions (cervical/axillary lymph nodes) should be done before attempting biopsy from mediastinal mass. Treatment includes steroids, radiation therapy for radiosensitive tumors, and early initiation of chemotherapy [22].

2.2.2 Cardiac Tamponade

Common causes are tumor involving pericardium, opportunistic infection in immunocompromised patients, or fibrosis secondary to previous radiation [23]. Common tumors that invade the pericardium are leukemia and lymphoma [23, 24]. Cause of neonatal pericardial effusion is cardiac hemangioma [25]. The classical presentation of cardiac tamponade is hypotension, increased jugular venous pressure, and subdued heart sounds. Children may present with tachycardia, chest pain, cough, dyspnea, and pulsus paradoxus. Chest X-ray shows a globular-shaped enlarged cardiac shadow, known as “water bottle” shape [26]. Echocardiography shows fluid around the heart and may also show thickening of the pericardium due to pericarditis or pericardial tumor. CT scan shows compression of the cardiac chambers by effusion, nodular lesions, thickening of the pericardium, or hemorrhage [27]. Supportive care for cardiac tamponade includes oxygen and patient positioning to maximize cardiac output. Percutaneous catheter drainage should be done immediately to relieve the symptoms [28].

2.3 Abdominal Oncologic Emergencies

2.3.1 Intestinal Obstruction and Intussusception

Common tumors that presents with intestinal obstruction are abdominal Burkett’s lymphoma, large renal/adrenal tumor, ovarian and colon tumors, sarcoma, and presacral teratoma [18]. Vinca alkaloids and narcotics can cause paralytic ileus. Children present with abdominal pain and bilious vomiting. Diagnostic radiologic studies should begin with supine, erect, and left lateral decubitus abdominal films, which shows multiple dilated loops of bowel with air–fluid levels [29]. With paralytic ileus, there is uniform dilatation of the entire small and large bowels. Malignant tumors (Burkitt lymphoma and carcinoid tumor) can present with intussusception [29]. Small-bowel obstruction is managed initially by keeping the patient nil orally and placing a nasogastric tube for decompression. Evaluation for the underlying etiology should proceed simultaneously and chemotherapy to be started early as the tumor in paediatric age group are chemosensitive.

2.3.2 Acute Pancreatitis

Acute pancreatitis in children is usually caused by drugs, like L-asparaginase, corticosteroids, 6-mercaptopurine, used in the treatment of ALL [30]. Patients typically present with severe abdominal pain, nausea, vomiting, and soon after starting L-asparaginase therapy. The diagnosis of acute pancreatitis is based on clinical and laboratory values of raised amylase and lipase levels. Ultrasound abdomen can be normal in mild acute pancreatitis; however, in severe cases, the pancreas is enlarged and hypoechoic [29]. CT shows focal or diffuse pancreatic enlargement and often to peripancreatic fluid collection. Early fluid resuscitation is critically important as patients lose a large amount of fluids due to third spacing. Strict input and output monitoring is essential to decide on the rate of fluid infusion. Nasojejunal feedings with a low-fat formulation should be initiated as and when patient's pain and anorexia resolves. Total parental nutrition may be required if caloric needs per day are not met with enteral feeding or if patient is not tolerating the oral feeds [31]. Patients should be started on broad-spectrum antibiotics as patients are usually immunocompromised and early in treatment phase of their cancer. Patients should be monitored for development of complications like pseudo cyst formation, necrosis, abscess, and hemorrhage [32].

2.4 Neutropenic Colitis

Neutropenic colitis is a necrotizing colitis that mostly involves the cecum, ascending colon, appendix, and terminal ileum, in neutropenic patients predominantly with hematologic malignancies [18].

The majority of children presents with abdominal pain, fever, abdominal tenderness, and diarrhea [33]. Child presents with these complaints typically at nadir neutrophil counts. USG abdomen and pelvis shows bowel wall thickening (>3 mm), pneumatosis intestinalis, and free fluid [33]. Conservative management includes—fluid management, pain control, broad-spectrum antibiotics to cover gram-negative pathogens, and clindamycin or metronidazole for gastrointestinal anaerobes and often antifungal agents [34]. Surgical intervention is required in following conditions: persistent gastrointestinal bleeding despite resolution of thrombocytopenia and correction of clotting abnormalities; presence of free air (as seen in CT abdomen); and uncontrolled sepsis from intestinal infarction [34].

3 Brain Metastases and Spinal Cord Compression

Brain metastases (BM) are common intracranial tumors and occur in 20% to 40% of all solid cancer patients [35]. The most frequent primaries contributing to brain metastasis are lung, breast, and melanoma (7%–16%).

3.1 Imaging

Magnetic resonance imaging (MRI) plain with contrast is the first line of investigation and is used for diagnosing and differentiating BM from other intracranial tumors. It is also helpful in assessing the response to treatment.

3.2 Treatment

There are multiple treatment options including surgical resection, radiation therapy, and/or chemotherapy. Choice of therapy is based on patient's prognosis or survival. Localized therapies (surgery, stereotactic radiosurgery) are considered for patients with better prognosis. The prognosis can be gauged from several prognostic scoring systems that have been developed. These include the Recursive Partitioning Analysis (RPA), Basic Score for BM (BSBM), Score Index for Radiosurgery (SIR), Golden Grading System (GGS), and Graded Prognostic Assessment (GPA) classification systems [36].

3.3 Surgery

Surgery plays a significant role in the management of BM. It helps in achieving decompression, thus provides instant relief of symptoms secondary to mass effect. In addition, it provides tissue for histopathological evaluation and for molecular analysis. The surgery for BM is indicated for patients who has ECOG PS 0–2, good prognosis, lesion below 3 cm, and lesion in accessible locations. However, surgery can be performed for large lesions, with significant mass effect, or symptomatic lesions, even for palliative purposes if clinically warranted.

The early randomized trials by Patchell et al. demonstrated complete resection at surgery as the best management strategy for single BM [37]. The patients with a single BM were randomized to surgery plus whole brain radiation therapy (WBRT) or biopsy plus WBRT. The results showed survival benefit to surgical resection (OS 40 weeks vs. 15 weeks, $p < 0.01$) and better local control. Subsequently, the same group studied single BM with complete surgical resection randomized to WBRT or observation. The post-surgery WBRT decreased intracranial failure from 70% to 18% ($p < 0.001$) and also reduced local recurrence from 46% to 10% ($p < 0.001$).

3.4 Adjuvant Radiotherapy

Since Patchell et al. [38] initial results, multiple series using improved stereotactic guidance, modern surgical techniques, and MR imaging have shown that the rate of recurrence post-surgery alone was reduced to 50%. To reduce postoperative recurrence, radiosurgery or radiotherapy is recommended. However, WBRT comes with substantial cost of neurocognitive decline and hence efforts to avoid it are considered.

In a randomized trial comparing WBRT to SRS, equivalent OS for postoperative SRS and WBRT (median OS: 12.2 vs.11.6 months, respectively; $p = 0.70$) were demonstrated. 85% patients post WBRT had cognitive deterioration at 6 months posttreatment as compared to only 52% with SRS

($p < 0.001$). Postoperative SRS is standard of care after surgically resected metastases. However, WBRT is associated with better surgical bed control rates at 12 months (81 vs 61%; $p < 0.001$).

3.5 One to Four BM

In a randomized study of two to four BM, all <2.5 cm with WBRT vs. WBRT plus SRS boost showed better control with SRS boost (100% vs. 8%) and survival (11 vs. 7.5 m) [39]. RTOG 95-08 randomized 300 patients similarly and showed improved local control at 1 year 71%–82% but no survival difference [40]. In patients with single BM or recursive partition analysis (RPA) Class I, SRS boost has shown improved survival from 4.9 to 6.5 months ($p = 0.39$) and 9.6 to 11.6 months ($p = 0.045$), respectively. When patients were analyzed by GPA score, it was found that patients with a high GPA (3.5–4) had improved survival irrespective of number of BMs. This study showed that SRS boost improves local control and OS, principally in patients with good performance status [40].

A Cochrane Database updated review for all three randomized trials ($n = 358$) showed that with the use of WBRT plus SRS, there was decrease in local failure (HR 0.27 95% CI 0.14–0.52), improved performance status scores and decreased steroid use (RR 0.64 CI 0.42–0.97). There was no difference in survival between the groups, though participants with single BM had significantly longer median survival in the WBRT plus SRS group ($p = 0.04$) [41].

In a phase III study (Aoyama et al.; $n = 132$), it was seen that local failure rates reduced from 76 to 47% by adding WBRT to SRS, in patients with four or less BM with size <3 cm [42]. However, survival of patients did not improve by adding WBRT [42]. In EORTC phase III study, patients with one to three BM who underwent SRS or surgery were randomized to WBRT or observation did not show any difference in survival between the groups [43]. An individual patient-level meta-analysis of the multiple studies showed that patients younger than 50 years of age had an improved survival with SRS alone compared to SRS plus WBRT (10 vs. 8.2 months, $p = 0.04$).

Above trials and analyses have standardized the treatment of patients with one to four BM. We have learned that there is no negative impact on the OS by eliminating WBRT, there is improved local control with SRS plus WBRT and the risk of neurocognitive decline is lower with SRS alone.

3.6 Neurocognitive Sparing

The neuroprotective drugs are being increasing used to preserve cognitive function for patients requiring WBRT. Memantine is an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, which has important roles in learning and memory. The RTOG 0614 explored memantine for reducing neurocognitive decline. In this phase III trial, there was a trend toward delayed recall improvement but did not reach statistical significance ($p = 0.059$). In addition, there was delayed time to cognitive decline, reduced rate of decline in memory, executive function, and processing speed [44].

3.7 More than Four Metastases

The optimal radiation modality for patients with 5–15 BM (SRS or WBRT) is not clear. Though multiple retrospective and prospective papers have already shown feasibility of SRS alone in patients with up to 10 BM. However, a randomized study by the Canadian Cancer Trials Group (CCTG)-lead North American intergroup trial is ongoing testing this. Yamamoto et al. prospective observational study of SRS alone for treatment of 5–0 BM showed that overall survival was similar between patients with 2–4 metastases as compared to 5–10 metastases with no difference in acute toxicities but this data needs validation in future studies.

3.8 Systemic Therapy

In general, the chemotherapy is not considered an effective mode of controlling BM due to limited penetration of BBB.

3.9 Medical Management with Targeted Therapy

Longer survival in metastatic patients treated with targeted therapy increasing chances of developing BM. It is also postulated that this relegates the brain as a “sanctuary” site in which undetected intracranial micromets are sheltered from systemic treatment that is unable to penetrate the “sanctuary” of the BBB (Her 2 Breast Cancer, BRAF mutant melanoma). Recently, some newer targeted agents are demonstrated to cross BBB and may help in controlling BM. Some of the data is listed in Table 1 [45].

3.10 Immunotherapy

Brain has long been viewed as an immune-privileged environment. Emerging clinical data also suggest existence of stimulation of peripheral T cells leading to antitumor effects in the brain across BBB by using immune checkpoint inhibitors. The immunotherapeutic agents like pembrolizumab have shown response rates of 20%–30% in patients with melanoma or nonsmall cell lung cancer (NSCLC) BM. The

Table 1 Targeted agents in BM

Targeted therapy	Primary malignancy	Level of evidence	Best available outcome
ALK-directed therapy			
Crizotinib	Nonsmall cell lung cancer	Subgroup phase 3	12-week DCR 85% vs. 45% with chemo
Ceritinib		Subgroup P2	RR: 45%
Alectinib		Pooled Ph2	RR: 64%
Brigatinib		Subgroup Ph2	RR: 78% vs. 29% with crizotinib
EGFR-directed therapy			
Erlotinib	Nonsmall cell lung cancer	Phase 2 Phase 3	PFS: 10.1 months alone, 60% RR with RT RT = Erlotnib: Med OS: 6.1 m
Osimertinib		Phase 3	PFS at 6 months: 87% vs. 71% (std E-TKI) PFS at 18 months: 58% vs. 40%
HER2-directed therapy			
Lapatinib + Capecitabine	Breast cancer	Phase 2	BM IC-RR: 66%
Neratinib + Capecitabine		Phase 2	12-month OS: 63%
BRAF-MEK			
Vemurafenib		Phase 2	RR: 18%
Dabrafenib	Melanoma	Phase 2	RR of 40% in Rx naïve and 30% in prev Rx
Dabrafenib + Trametinib		Phase 2	RR: 44–59%
VEGF pathway Bevacizumab + Carboplatin	Breast cancer	Phase 2	RR: 45%

nivolumab and ipilimumab combination had shown a response rate of 55% in patients with melanoma BM [46]. Similarly, prolonged control rates are reported in lung, melanoma, RCC BM when patients on immunotherapy and received various types of radiotherapy for BM. At present, more data are needed to confirm these results, determine mechanisms of efficacy and resistance and for concrete recommendations.

3.11 Spinal Cord Compression

Epidural spinal cord compression is one of the commonest methods of neoplastic spinal cord compression. The importance of recognizing and acting fast is imperative as neurological signs like paraplegia or paraparesis can be reversed if treatment is started within 48 h of their occurrence. MRI spine is an important investigation guiding treatment. The selection of treatment needs to take into account three factors.

1. Mechanical stability of the spine
2. Radiosensitivity of the neoplasm
3. Overall prognosis of the disease

3.11.1 Mechanical Stability of the Spine

It should be assessed using Spine Instability Neoplastic score [47]. If we have a score of 7 or more than there is spinal instability and it warrants surgical consultation. Irrespective of the radiosensitive nature of the disease in presence of spine instability surgical intervention is required [48]. The score has a sensitivity and specificity of 96 and 80%, respectively, for predicting unstable lesions.

3.12 Radiosensitivity of the Neoplasm

The choice between surgical or radiation modality rests on this aspect. Radioresistant tumors should be addressed by surgical methods.

3.12.1 Overall Prognosis of the Disease

The key question is whether we should aggressively treat the patient or not. A consultation with treating medical oncologists and briefing on the expected prognosis should help in this decision making. It is better than keeping a survival cut off the focus should be on whether a patient will be able to recover postoperative or post radiation or not. In addition to these points general antiedema measures should be provided like glucocorticoids, pain management, venous thromboembolism prophylaxis, and palliative care consultation.

4 Febrile Neutropenia

4.1 Definition

Febrile neutropenia is defined as single oral temperature measurement of >101 °F or a temperature of 100.4 °F sustained over 1 h, with an absolute neutrophil count (ANC) of <500 cells/mL, or an ANC that is expected to decrease to <500 cells/mL in the next 48 h [49].

4.2 Epidemiology

Febrile neutropenia is the most common life-threatening complication of cancer therapy. The frequency of febrile neutropenia is higher in patients with hematological malignancy than those with solid tumors [50]. In high-risk febrile neutropenic patients, major complications (e.g., hypotension; acute renal, respiratory, or heart failure) occur in approximately 25%–30% of patients and mortality is approximately 11% [50].

Risk of FN is higher in case of low first-cycle nadir neutrophil count, prior history of neutropenic fever, prolonged duration of neutropenia, the magnitude of neutropenia, chemotherapy intensity, older age, female sex, low performance status, low albumin level, associated anemia, bone marrow involvement, and preexisting organ dysfunction [51].

4.3 Pathophysiology

The causative organisms could be gram positive, gram negative, or anaerobes. The most common gram-negative organisms in this setting are *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa*. The most common gram-positive organisms are coagulase-negative staphylococci, *Staphylococcus aureus*, viridans group streptococci, and *Enterococcus* species. Anaerobes are found in <5% of cases, and fungi (predominantly *Candida* and *Aspergillus* species) are found in 2%–10% of at-risk patients (i.e., those with severe, protracted neutropenia [neutrophil count <100 cells/mL for more than 7 days]), a history of corticosteroid use; older age; status post-intensive chemotherapy; central catheters; advanced-stage disease; or evidence of tissue damage) [52].

4.4 Differential Diagnosis

Common causes of fever in cancer patients that need to be differentiated from FN are drug-induced fever, tumor-associated fever, thromboembolism, and paraneoplastic syndromes.

Neutropenic patients are a heterogeneous population, with subgroups with varying risks regarding response to initial therapy, development of serious medical complications, and mortality. Various scoring systems are available that can differentiate patients into low- or high-risk group and guide management of patient with febrile neutropenia. The most commonly used scoring system in clinical practice is MASCC score [53], which accurately identifies patients, at the time of presentation into low risk and high risk of complications.

The following investigations should be done in patients with FN:

1. Complete blood counts with differentials
2. Kidney function tests and liver functions tests
3. *Blood cultures and fungal cultures:* Peripheral blood culture should be collected before starting intravenous antibiotics. If patient has central venous catheter, then concomitant blood cultures should be drawn peripherally and from central venous catheters. Differential time to positivity of >120 min between the central venous catheter and peripheral cultures is diagnostic of catheter-related infection. Fungal cultures should be sent in patients with a prior history of fungal infections, patients who are on steroids, patients with indwelling catheters or in case of radiological examination suggestive of fungal infections. Central venous catheters should be removed in the setting of catheter-related infections or fungemia [54].
4. *Chest X-rays /echocardiography:* Chest X-ray should be done in all patients with FN especially those who requires hospital admission as these patients may not have signs and symptoms of respiratory infections. Echocardiogram should be considered in patients with clinical signs and symptoms of cardiac failure, in case of persistent fever when no other focus is found, persistent bacteremia due to an organism such as enterococci or viridans group streptococci, and those with persistent fungemia.
5. *Stool/urine cultures:* Urine routine examination may not show pus cells in neutropenic patients, urine culture must be done irrespective of urine routine report if urinary tract infection is clinically suspected. If patients present with loose stools or signs suggestive of colitis, then stool culture must be sent.

Common organisms causing colitis are *Clostridium difficile* and other pathogens such as *Salmonella*, *Shigella*, *Campylobacter*, norovirus, cytomegalovirus, or rotavirus.

4.5 CECT (Thorax and Abdomen and Pelvis)

Chest CT scans are more sensitive than a chest X-ray and demonstrate the presence of pulmonary infiltrates far more frequently in this setting [55].

4.6 Management

4.6.1 Primary Options

The first dose of antibiotics should be administered within 1 h of a neutropenic patient presenting with fever [49, 56].

At-risk patients include those with severe, protracted neutropenia; with a history of corticosteroid use; older age (>65 years); status post-intensive chemotherapy; with central catheters; with more advanced stage of disease; and with evidence of tissue damage [52].

Empiric monotherapy with piperacillin/tazobactam, cefaperazone/sulbactam, cefepime is an acceptable option. Combination therapy with an aminoglycoside can be considered, with early discontinuation of the aminoglycoside if cultures do not reveal evidence of a drug-resistant pathogen infection. The choice of antibiotics depends on local institutional bacterial susceptibilities [57]. Combination therapy with cefaperazone/sulbactam and an aminoglycoside may be preferable in high-risk patients with prolonged neutropenia [56]. Once antibiotics are started, the median time to clinical response is 5–7 days, and antibiotics do not need to be changed despite persistence of fever for the first 3–5 days [58].

Antibiotics that cover gram-positive organisms should be started if there is evidence of grade III/IV mucositis, past history of blood infection with gram-positive organism, patients who presents with hypotension, cellulitis or if there is radiological evidence of staphylococcus pneumonia. The Infectious Disease Society of America (IDSA) guidelines note that the presence of a central venous catheter is not an indication for empirical vancomycin [49].

In patients with documented infections, the duration of therapy depends on the specific organism and site of infection. Antibiotics may be continued for the duration of neutropenia (i.e., until absolute neutrophil count is ≥500 cells/mL), or longer if clinically necessary (10–14 days of treatment is usually sufficient for most infections) [49].

In patients with negative blood cultures and with an absolute neutrophil count ≤500 cells/mL, antibiotic therapy can be discontinued provided that they have been afebrile for 5–7 days and have no complications (the exception to this recommendation is high-risk patients with leukaemia, where antibiotic therapy is often continued for up to 10 days or until the absolute neutrophil count is ≥500 cells/mL) [56].

The use of empirical granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with febrile neutropenia is typically not recommended except in: high-risk patients with pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), invasive fungal infection, uncontrolled primary disease, or in patients who are persistently febrile (>10 days), have profound neutropenia (<100 cells/mL), are age >65 years, or were hospitalized at the time of fever development [59].

For low-risk patients who are candidates for outpatient management (i.e., those with solid tumors, expected neutropenia <7 days, stable vital signs, adherence to treatment, no organ dysfunction, tolerance of oral medications and fluids, residence ≤1 h from a clinic or hospital, and telephone and transport access), oral therapy with a fluoroquinolone (e.g., ciprofloxacin, levofloxacin, and moxifloxacin) plus amoxicillin/clavulanate (or clindamycin if the patient is penicillin allergic) is recommended [60, 61].

The choice of antifungal is often dictated by the resistance profile of the institution, risk factors for aspergillosis (patients on long term steroids, prolonged neutropenia), and the severity of illness: for example, more aggressive treatment with voriconazole or amphotericin-B if the patient is critically ill [49].

4.6.2 Prophylactic Use of GCSF

Guidelines from the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Organisation for Research and Treatment of Cancer (EORTC) recommend the use of granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients at >20% risk for developing febrile neutropenia based on age, comorbid illness, disease characteristics, and myelotoxicity of the chemotherapy regimen [62, 63]. Meta-analyses have shown that granulocyte colony-stimulating factor (G-CSF) prophylaxis reduces the incidence of febrile neutropenia in adults undergoing chemotherapy for solid tumors and lymphoma [64].

4.6.3 Antibacterial and Antifungal Prophylaxis

Joint ASCO and Infectious Diseases Society of America (IDSA) guidelines recommend antibiotic prophylaxis with a fluoroquinolone for patients at high risk for febrile neutropenia or profound, protracted neutropenia, such as patients with acute myeloid leukemia, myelodysplastic syndromes, or hematopoietic stem-cell transplantation treated with myeloablative conditioning regimens [65].

4.6.4 Secondary Prevention

Patients with a history of febrile neutropenia are at risk for subsequent episodes of febrile neutropenia, and many professional societies including the American Society of Clinical Oncology (ASCO), the National Cancer Center Network (NCCN), and the European Organisation for Research and Treatment of Cancer (EORTC) recommend the routine use of colony-stimulating factors as secondary prophylaxis against febrile neutropenia with subsequent cycles of chemotherapy [59].

4.7 Complications

1. **Mortality:** Mortality from febrile neutropenia has decreased to less than 10% among patients who receive antibiotics promptly [66]. In contrast, mortality in low-

risk, febrile neutropenic patients is 1%–2% [67]. Mortality risk is higher in patients who present with hypotension and documented bacteremia (as high as 24%–82%) [68]. It is also increased in patients with pneumonia, uncontrolled cancer, polymicrobial infections, and older age [69].
2. **Clostridium difficile**
3. **Antibiotic-induced fungal overgrowth**
4. **Emergence of multidrug resistant infections**

4.8 Prognosis

Although mortality from febrile neutropenia has steadily declined, the condition is still associated with considerable morbidity and mortality. Approximately 20% to 30% of patients with febrile neutropenia present with complications that require in-hospital management [56].

5 Hypercalcemia of Malignancy

Hypercalcemia occurs in 20%–30% of patients with cancer [70, 71]. Common cancers that are associated with hypercalcemia are renal cancer, squamous cell carcinoma, breast cancer, ovarian cancer, endometrial cancer, and human T-lymphotropic virus-associated lymphoma [70, 72, 73].

5.1 Pathophysiology

Hypercalcemia is caused by three mechanisms:

1. Humoral—mediated by parathyroid hormone-related peptide (PTHrP) leads to activation of osteoclastic bone resorption and suppression of osteoblastic bone formation. This results in skeletal release of calcium and subsequent hypercalcaemia. PTHrP also acts at the level of the kidney to reduce calcium clearance, as well as to reduce the renal phosphorus threshold, leading to hyperphosphaturia and hypophosphataemia [70, 72].
2. Local osteolytic hypercalcemia: in the setting of malignancy with widespread skeletal involvement, local release of cytokines (e.g., IL-1 and IL-6), chemokines, and PTHrP leads to increased osteoclastic bone resorption and to increased release of calcium into the serum that overwhelms the kidney's capacity to clear calcium [72].
3. Hypercalcemia mediated by increased calcitriol (1,25 dihydroxy vitamin D) synthesis or ectopic parathyroid hormone secretion [73].

5.2 Diagnosis

Common presenting symptoms are gastrointestinal disturbance (anorexia, nausea, and constipation), polydipsia, polyuria, and bone pain. Some patients do present with fatigue, confusion, stupor, and coma [70, 72, 73]. Patients may have poor skin turgor or dry mucous membranes due to dehydration. However, hypercalcemia may not be associated with any specific physical examination findings. A thorough medication history to evaluate for use of medications that may cause or worsen hypercalcemia (thiazide diuretics, lithium, calcium, over-the-counter antacids, and large doses of vitamin D) should be undertaken [73].

5.2.1 Laboratory Evaluation

The following investigations should be sent when hypercalcemia is suspected—serum calcium, ionized calcium, renal function tests, serum albumin, serum phosphorous, serum parathyroid levels/parathyroid hormone-related peptide, resting ECG to assess for a shortened QT interval, and dysrhythmias.

5.2.2 Radiology Evaluation

A skeletal survey in patients in whom multiple myeloma, bone metastases, or leukemia are suspected. Chest X-ray to assess for lung cancer, sarcoidosis, or tuberculosis. Further imaging should be ordered, according to the suspected cancer or condition and the anatomical region involved [72].

5.3 Management

The treatment for hypercalcemia of malignancy depends on the underlying pathophysiology and severity of hypercalcemia. Hypercalcemia of malignancy resolves with definitive anticancer therapy.

5.3.1 Asymptomatic Patients with Mild Hypercalcemia

Serum Ca level of 10.5–12 mg/dL is defined as mild hypercalcemia. Such patients do not require immediate treatment, supportive measures include increase oral water intake, with hold calcium supplements IV or oral, and discontinuation of drugs causing hypercalcemia (vitamin D thiazide diuretics).

5.3.2 Symptomatic Patients with Serum Ca Levels Greater than 12 Mg/dL

Symptomatic patients with serum Ca levels greater than 12 mg/dL or patients with hypercalcemic crisis (serum calcium more than 14 mg/dL) should be admitted immediately and started on aggressive therapy that includes

1. Hydration: Most patients with hypercalcemia are dehydrated due decreased oral fluid intake resulting from nausea and vomiting and also secondary to renal dysfunction induced by hypercalcemia. Therefore, initial management is volume expansion with intravenous fluids, which increases the glomerular filtration rate and also excretion of calcium. Normal saline should be given at rate of 200 mL/h depending on renal function and dehydration status. Hydration should be continued until patient's serum calcium level is corrected within the normal range [73].
2. Diuretics: Once intravascular volume has been repleted, low-dose of furosemide (20–40 mg IV) every 12 h should be given which will further reduce the calcium level. It blocks calcium reabsorption in the loop of Henle and also increase urine output thus preventing fluid overload secondary to hyperhydration [73].
3. Bisphosphonates: Bisphosphonates are the most effective agents for treating malignancy-associated hypercalcaemia. Bisphosphonates effectively block osteoclastic bone resorption. Therapy should be instituted immediately upon diagnosis because response generally takes 2–4 days. Zoledronic acid is usually preferred and administered as a single dose [74]. Vitamin D should be measured (and corrected if deficient) prior to intravenous bisphosphonate therapy to avoid the risk of hypocalcemia. Regular monitoring of calcium levels is also important. If hypercalcemia is improved with the initial dose, but serum calcium levels begin to increase again, the dose may be repeated after 7 days. Denosumab is a monoclonal antibody directed against the receptor activator of nuclear factor-KappaB ligand (RANKL); it reduces osteoclast differentiation and bone resorption and is considered for patients who has hypercalcemia refractory to zoledronic acid.
4. Calcitonin: Calcitonin interferes with osteoclastic bone resorption [70]. It may cause a more rapid correction of hypercalcemia than bisphosphonates [75, 76]. The clinical utility of calcitonin is limited by its transient effect and availability [75, 76]. Potential adverse effects include flushing and nausea. Calcitonin may be used in the first 24–48 h following bisphosphonate administration to transiently reverse hypercalcaemia while awaiting the therapeutic effect of bisphosphonate therapy.
5. Dialysis can be considered in patients who have cancers that are likely to respond to therapy, but in whom renal and cardiac function limits utilization of intravenous hydration or accepted pharmacological therapy [77].

5.3.3 Vitamin D (1,25-Dihydroxyvitamin D)-Mediated Hypercalcaemia

Glucocorticoid therapy is efficacious in treating calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia. No guidelines with respect to dosing and duration of therapy exist [70].

5.3.4 Ectopic Parathyroid Hormone Production

Removal of primary malignancy/ectopic parathyroid hormone-secreting source can reverse hypercalcemia [78].

5.4 Monitoring

The nadir in serum calcium levels following bisphosphonate administration typically occurs within 7 days. Responses last for 1–4 weeks [76]. Serial monitoring of calcium is, therefore, important. Eradication of underlying malignancy is crucial for continued maintenance of normal calcium level.

6 Thrombocytopenia

Thrombocytopenia is generally defined as platelet counts less than 150 * 10^9/L. It is further subdivided into mild (platelet count 100,000 to 150,000/microL), moderate (50,000 to 99,000/microL), and severe (<50,000/microL) [79–81]. Thrombocytopenia develops due to either increased destruction or decreased production of platelets. Increased loss of platelets happens in conditions like disseminated intravascular coagulation, thrombotic microangiopathies, or immune-mediated destruction of platelets [82, 83]. Decreased production happens in cases of bone marrow failure like leukemia, myelodysplastic syndromes, aplastic anemia, or chemotherapy induced.

6.1 History and Physical Examination

A thorough history and physical examination facilitate the diagnosis. Important aspects include the following:

- Family history of bleeding disorders and/or thrombocytopenia
- History of bleeding (e.g., petechiae, ecchymoses, epistaxis, gingival bleeding, hematemesis, melena, and heavy menstrual bleeding)
- Disease history like malignancies, infections, and autoimmune disorders [84]
- Medication exposures—e.g., aspirin, nonsteroidal anti-inflammatory drugs, and herbal remedies [81]
- Recent travel history for malaria, dengue fever, viral infections
- Recent transfusions/vaccinations [85]

6.2 Physical Examination

Physical examination should focus on site of bleeding, severity of bleeding, and other abnormalities on general examination like lymphadenopathy, hepatosplenomegaly, or skeletal abnormalities. Patients with thrombocytopenia presents with mucocutaneous bleeding, while the bleeding in joints or soft tissues suggests coagulation abnormalities, like DIC. The presence of skin necrosis should raise suspicion of heparin-induced thrombocytopenia (HIT).

6.3 Laboratory Testing

Peripheral blood smear: remains the most important investigation in diagnostic approach to thrombocytopenia. All three blood cell lineages should be assessed carefully, we can differentiate whether it is thrombotic microangiopathy (RBC fragmentation) or acute leukemia (blasts). Platelet clumping suggests the possibility of pseudo thrombocytopenia.

6.3.1 RBC and WBC Abnormalities

Abnormal RBC and WBC morphologies may suggest a specific condition. Examples include the following:

- Schistocytes suggest a microangiopathic process (e.g., DIC, TTP, HUS, and DITMA).
- Nucleated RBCs, and Howell–Jolly bodies, may be seen post-splenectomy or occasionally in patients with poor splenic function.
- Spherocytes suggest immune-mediated hemolytic anemia or hereditary spherocytosis.
- Leucoerythroblastic picture, teardrop cells, nucleated RBCs, or immature granulocytes suggest an infiltrative process in the bone marrow.
- Leukocytosis with a predominance of bands (left shift) and/or toxic granulations suggests infection
- Immature WBCs (e.g., myeloblasts) or dysplastic WBCs suggest leukemia or myelodysplasia.
- Multilobed/hypersegmented neutrophils (i.e., >5 lobes) suggest a megaloblastic process (e.g., B12/folate/copper deficiency).
- Combined anemia and thrombocytopenia can be seen if there has been longstanding bleeding (e.g., gastrointestinal) and also raise the possibility of systemic disorders.

A basic laboratory evaluation should include liver and renal function tests, a coagulation profile with D-dimers, serological testing (HIV and HCV), and measurement of lactate dehydrogenase.

Second stage of investigations should be impelled by clinical findings and the results of the peripheral blood smear. A bone marrow aspirate and biopsy should be done if cause of thrombocytopenia is unclear. If fraction of platelets in bone marrow aspirate are increased, it suggests hyper destructive thrombocytopenia (e.g., immune thrombocytopenia). If fraction of platelets in bone marrow aspirate are decreased or shows reticulated platelets, this suggest bone marrow failure [86, 87].

6.4 Management

Early recognition of the etiology of thrombocytopenia is crucial for the timely management of patients. The initial approach is based on the patient's history, physical examination, and the peripheral blood smear findings. The most common causes of thrombocytopenia are immune thrombocytopenia (ITP) and drug-induced thrombocytopenia (DTIP). Clinically, DITP can be confused with ITP and only a careful history taking can help in the correct diagnosis [88]. DITP should also be considered when patients have recurrent episodes of thrombocytopenia with rapid recovery.

6.4.1 Treatment of ITP

The decision to start therapy is based on bleeding tendency and on absolute platelet count. First line of therapy is steroids, and prednisolone at a dose of 1 to 2 mg/kg/day is given for 2 weeks. Once response is achieved, weekly dose reduction is done until a dose of 0.5 mg/kg is reached and then slow tapering by 5 mg/week [89]. In case of severe bleeding, immunoglobulins at a dose of 0.4–1 g/kg/day should be given as it leads to faster recovery of platelets [90]. Second-line therapy is indicated if there is only partial response to first-line therapy or patients develops thrombocytopenia again after an initial response. Rituximab 375 mg/m^2 per week for 4 weeks has shown long-term response rates of 40% [91]. The other drugs can be considered are cyclophosphamide, cyclosporin, and mycophenolate mofetil if there is no response to above therapies [92]. Newer therapies include thrombopoietin receptor agonist, romiplostim and eltrombopag, which have a response rates of 30%–40% and these medications are more effective in patients with chronic ITP [93]. Splenectomy is indicated patients who have no or only an insufficient response to all other treatment modalities, it has the highest rate of remissions from all ITP therapies, nearly 60% of patients will achieve complete response [94]. All patients must preoperatively receive Haemophilus influenzae b, pneumococcal, and meningococcal vaccinations before spleenectomy [95].

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Pain Management

Raghu S. Thota and Parmanand Jain

Abbreviations

APS	American Pain Society
CPPS	Cancer pain prognostic scale
EDSS	Edmonton Staging System
ESAS	Edmonton Symptom Assessment System
IASP	International Association for the Study of Pain
IV	Intravenous
MDASI	M. D. Anderson Symptom Inventory
NCCN	National Comprehensive Cancer Network
NSAID	Nonsteroidal anti-inflammatory drug

1 Introduction

The prevalence of cancer is rising globally, and in most countries, the disease is presenting for treatment late, as an incurable illness. Commonly patients with solid tumors present as asymptomatic masses. Around 15% of patients with nonmetastatic cancer have pain. Pain is considered as an independent predictor of disease progression. With better understanding of pain pathophysiology and underlying nociception, a great promise for optimum pain therapeutics is fast evolving. The rapid development of palliative concept world over has enhanced awareness of the long underreported and undertreated problem. Patients now have better access to pain specialists in western countries, but many patients in developing countries in need of pain management do not have even easy access to oral opioids. Inadequately treated pain continues to be a huge burden on the patients, healthcare system and society at large.

2 Pain as a Symptom in Oncology

Pain as symptom is a more complex which affects a person at all stages of the disease physically, psychosocially and financially. In 2008, the International Association for the Study of Pain (IASP) stated: “for the more than 10 million people worldwide who are diagnosed with some form of cancer each year, pain associated with their condition is a serious concern. The consequences of unrelieved cancer pain are devastating” [1].Cancer pain is a complex symptom which affects person’s life, including activities of daily living, psychological and emotional status and social interactions as well. The prevalence of cancer pain varies widely at different stages of cancer and its treatment (Fig. 1). The estimated pooled prevalence of cancer pain in populations undergoing curative treatment is 39.3% (95% CI 33.3–45.3); 55.0% (95% CI 45.9–64.2) during anticancer treatment; 66.4% (95% CI 58.1–74.7) in advanced, metastatic, or terminal disease and 50.7% (95% CI 37.2–64.1) in studies that included all cancer stages [2]. Pain is one of the most dreaded symptoms in cancer; regrettably, it is often undertreated. Even with the greater availability of pain medications, it continues to be moderate to severe in more than 50% of cancer patients [2]. Of all the patients with advanced stage cancer who experience pain, 70% of pain is associated with the primary cancer, and 20% is associated with cancer treatments and remaining 10% will have pain from other chronic pain syndromes [3]. Of the various pain syndromes, visceral cancers had the highest prevalence of pain followed by head and neck cancer pain and skeletal metastases [4]. In a 10-year prospective study, Zechet et al. [5] reported on localization, etiology and type of pain syndromes. Pain was most often localized to lower back, lumbar spine, sacrum and coccyx (36%) followed by abdominal region (27%), thoracic region (24%) and lower limbs (22%). In 85% of patients, cancer was the most common cause of

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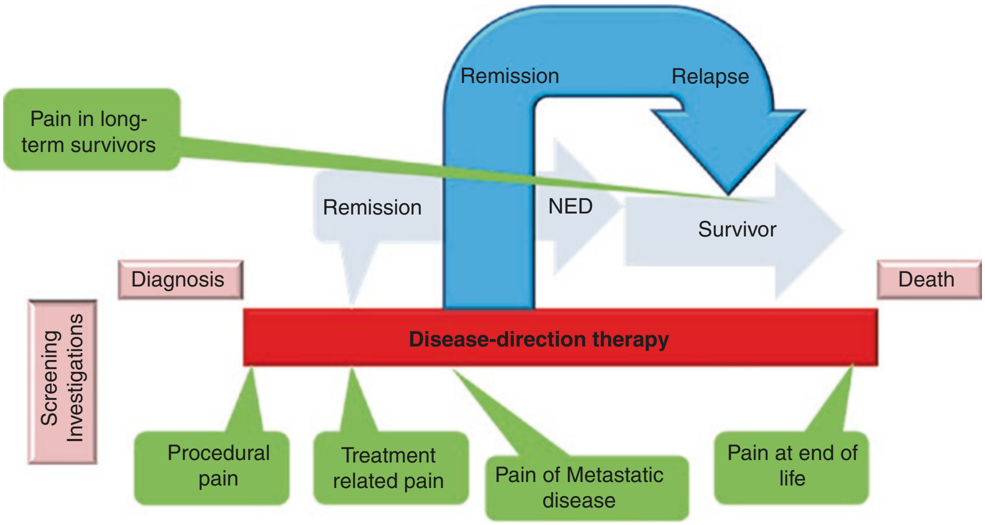

Fig. 1 Cancer disease and the pain at different aspects of the course. NED, no evidence of disease

pain. Caraceni et al. [6] published a study involving prospective, cross-sectional, international survey of pain specialists and their patients which also incorporated data from Tata Memorial Centre, Mumbai, India. They reported that somatic pain occurred in 39.7% of patients with major pain syndromes comprised of skeletal lesions (41.7%), other types were visceral lesions (28.1%) and those with soft tissue infiltration (27.8%). Karnofsky performance score was <70% in more than 76% of patients. A large majority of patients (92.5%) had one or more type of pain and 20.8% of patients suffered pain due to cancer therapies.

Comprehensive assessment and reassessment of pain is the key to successful cancer pain management [7]. Multidisciplinary approach is the best way to manage cancer pain. In patients undergoing active therapy, the goal of cancer pain management is to provide them with sufficient relief to tolerate the diagnostic and therapeutic procedures required for the treatment. Opioids remain crucial to the management of cancer pain. However, obstacles to global pain relief remain primarily issues of access to clinicians and medications which are scarce in developing countries.

2.1 Barriers to Pain Relief

1. Government and system barriers, such as legislation limiting the availability of or access to opioids [8], or lack of effective policies on pain management and palliative care [9];
2. Physician barriers, such as inadequate education around pain assessment and management, concerns about the risk of respiratory depression or excessive sedation [10] and "opiophobia" [11]; and
3. Patient barriers, such fear of addiction, the belief that "good" patients do not complain about pain, worry that treatment implies the final stages of life and concern about side effects [12, 13].

As per the WHO, over 80% of the world's population is inadequately treated for moderate to severe pain [14]. It is equally important to control symptoms like psychological distress and the entire pain experience other than just pain.

3 Pathophysiology of Cancer Pain

Cancer pain shares the same neuropathophysiological pathways as noncancer pain. The molecular complexity of cancer pain is one of the reason for poor cancer pain control [15]. Cancer pain is often a mixed pain, and it involves inflammatory, neuropathic, ischemic and compressive mechanisms at multiple sites [16]. Most of the knowledge about cancer pain is currently based on preclinical models of cancer-induced bone pain [17]. Inflammatory infiltration of the tumor occurs and various cytokines and inflammatory pain mediators from the cancer cells and from a potential necrotic center in larger tumors are released [18]. There is a direct damage to the sensory nerves by infiltration or compression of tumor cells, or by remodeling in the local microenvironment causing hyperinnervation or denervation of the bone, or stretching of the densely innervated periosteum.

Cancer pain is classified into various types (Table 1).

Cancer pain can be classified as pain due to tumor, cancer treatment or unrelated to it [19]:

- **Tumor-related pain:** Pain may be the major symptom, prompting medical consultation and the diagnosis of cancer. Recurrent pain during the course of illness or after successful therapy has the immediate implication of recurrent disease.
- **Pain due to cancer therapy:** Postsurgery pain like phantom limb pain, postthoracotomy or postmastectomy pain, postchemotherapy pain or pains due to radiation neuropathy are few of the examples.

- **Pain unrelated to cancer:** Patients may have pain due to diabetic neuropathy, postherpetic neuralgia, cardiac pain or joint pain due to osteoarthritis.

Table 1 Classifications of cancer pain

Etiologic classification	• Primarily caused by cancer (e.g., metastatic bone pain) • Treatment of cancer (e.g., postthoracotomy pain, chemotherapy induced peripheral neuropathy, radiation induced mucositis) • Debility (postherpetic neuralgia) • Concurrent pathology (e.g., osteoarthritis)
Pathophysiologic classification	• Nociceptive (somatic, visceral) • Neuropathic • Mixed pathophysiology • Psychogenic
Location of cancer pain syndromes	• Head and neck pain • Chest wall syndromes • Vertebral and radicular pain • Abdominal or pelvic pain • Extremity pain (e.g., brachial plexopathy or bony spread)
Temporal classification	• Acute • Breakthrough • Chronic
Severity-based classification	• Mild • Moderate • Severe

Based on temporal distribution, pain is classified as Acute, breakthrough and chronic pain [19]. Acute pain is a well-defined pain with acute onset, with physical signs and hyperactivity of autonomic nervous system.

Breakthrough pain is a sudden flare-up of pain in patients whose baseline pain is well controlled on a by-the-clock analgesic [20, 21].

Chronic pain is persistence of pain for more than 3 months and is associated with significant changes in personality, lifestyle and functional ability.

4 Evaluation and Grading of Cancer Pain

Clinical practice guidelines developed by the National Comprehensive Cancer Network (NCCN) [22] and American Pain Society (APS) [23] emphasize the essential practice of comprehensive pain assessment. Comprehensive overview of the pain assessment process is shown in Fig. 2.

Core elements of initial assessment [24]:

- A detailed history of pain.
- A psychosocial assessment.
- A physical examination.
- Diagnostic evaluation of common cancer pain syndromes.

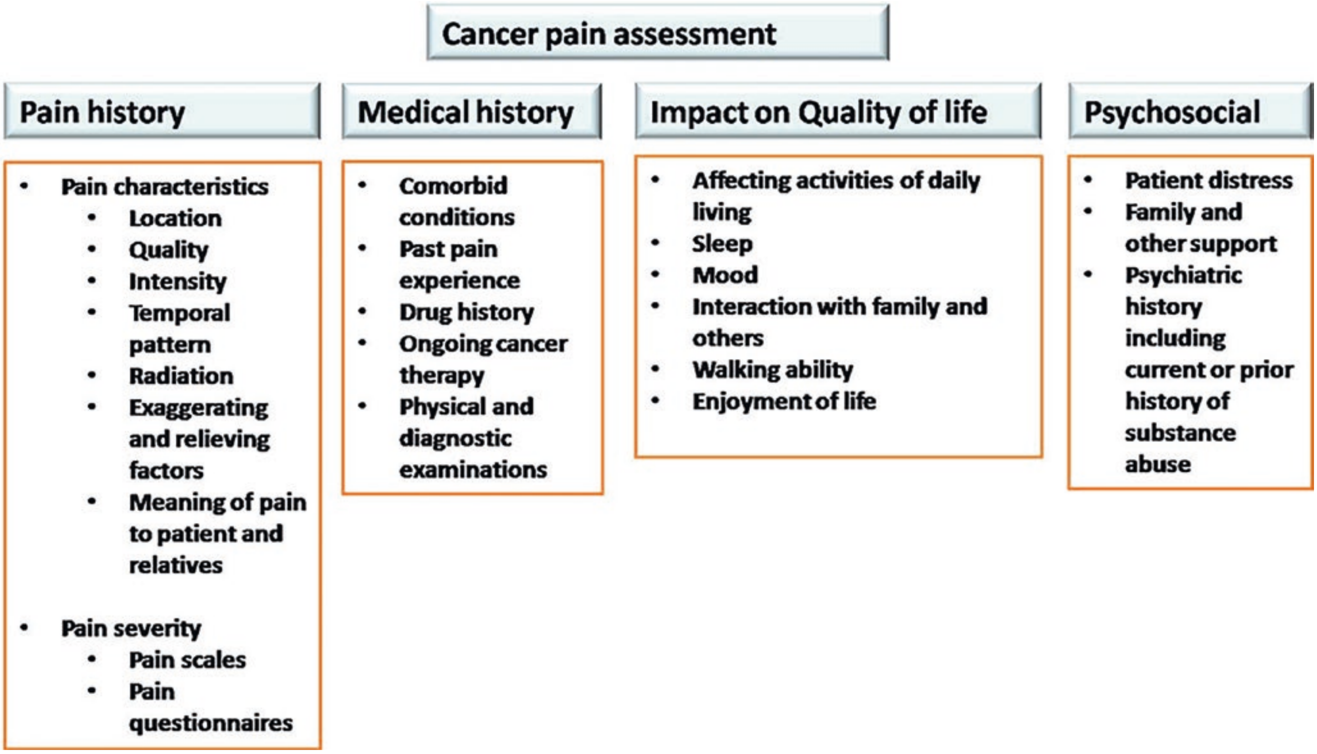
Cancer pain assessment
Pain history
Medical history
Impact on Quality of life
Psychosocial
• Pain characteristics
• Location
• Quality
• Intensity
• Temporal pattern
• Radiation
• Exaggerating and relieving factors
• Meaning of pain to patient and relatives
• Pain severity
• Pain scales
• Pain questionnaires
• Comorbid conditions
• Past pain experience
• Drug history
• Ongoing cancer therapy
• Physical and diagnostic examinations
• Affecting activities of daily living
• Sleep
• Mood
• Interaction with family and others
• Walking ability
• Enjoyment of life
• Patient distress
• Family and other support
• Psychiatric history including current or prior history of substance abuse

Fig. 2 Comprehensive cancer pain assessment

Table 2 Cardinal features of pain assessment

Location	Where does it hurt? Use a body outline chart for precision, which is easy for patients to use. Cancer patients frequently have many pains—elicit a description for each (see Fig. 2).
Quality	What does it feel like? Something like "shooting, burning, pins and needles" helps diagnose a neuropathic component. Describe each separate pain that the patient is experiencing.
Intensity	How bad is it? Use a scoring system. (a) Numerical scale: For example, 0–10 where 10 is the "worst possible pain" (see Fig. 3) (b) Visual analog scale in which a patient indicates pain with a mark on a 100-mm line (horizontal or vertical) delimited by descriptors (none to worst possible to pain). Pain is reported as the measurement, for example, 67 (see Fig. 3) (c) Word scale: Particularly good for concrete thinkers who cannot describe pain in terms of a number (see Fig. 3). (d) Faces scale: Particularly useful for children, the elderly, and those who do not speak your language (see Fig. 3).
Temporal pattern	When does it occur (including impact on sleep)? How long does it last?
Radiation	Where does the pain go?
Exacerbating and relieving factors	What makes it better? What makes it worse? What medications are you taking for the pain (prescription and over the counter)? What effect do they have?
Meaning	What does the pain mean to you? Also what it means to their family. Inquire about the emotional, social and spiritual dimensions.

The evaluation begins with a thorough history of pain and the malignancy and other comorbid conditions. It is also important to take history of the treatment of malignancy.

A critical component for defining the appropriate therapeutic strategy for each individual patient is adequate clinical assessment of pain. Always believe the patient's complaint of pain. Follow the seven cardinal features (Table 2, Fig. 3) of pain assessment [25]:

Pain also has a major impact on quality of life; thus, it is also necessary and essential to evaluate the effects of pain on physical and psychosocial well-being as well the spiritual effects on a patient's life. Since pain is multidimensional which affects the sensory and affective components in addition to intensity, there are many standardized pain questionnaires available that assess pain severity and other dimensions of pain (Brief Pain Inventory, McGill Pain Questionnaire, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire).

It is very important to ask history of the ongoing oncologic treatment including current and prior chemotherapy, radiation therapy and surgery, as most of the cancer pain is due to the cancer itself and the ongoing cancer therapy helps us to understand the pain pathophysiology to provide better pain management.

Cancer patients with pain usually have symptoms other than pain like fatigue, weakness, cachexia and cognitive deficits (most often due to cancer itself) [26].

Various tools like M. D. Anderson Symptom Inventory (MDASI) or the Edmonton Symptom Assessment System (ESAS) may be used to assess the presence and intensity of symptoms [27, 28].

It is of utmost importance to find out about the other significant illnesses and conditions, as we need to be careful and cautious when prescribing certain pharmacological agents (e.g., NSAIDs in CKD patients) and performing pain interventions (e.g., patient on anticoagulants for deep vein thrombosis).

It is important to undertake a careful medical and neurologic examination, as in one retrospective study they found that two-thirds of the patients had new and often treatable pathology diagnosed as a result of a neurological evaluation [29].

A review of the appropriate diagnostic studies: CT scan, MRI, bone scan and tumor markers often help to differentiate the primary site of the tumor and the metastatic involvement, as well as assess disease progression.

A pre-existing chronic pain experience has been strongly associated with suffering and is important to understand the unique patient experience, which often include religious beliefs and cultural influences, on the expression or treatment of pain [30].

It is very important to individualize the therapeutic approaches and discuss in advance directives with patient and family.

The Edmonton Staging System (EDSS) [27] provides a clinical staging system for cancer pain. The system allows accurate prediction of the outcome of patients with cancer pain. It has an excellent sensitivity (>90%), but poor specificity (<50%) [31]. The cancer pain prognostic scale (CPPS) proposed by Hwang and others [32] is an excellent tool for the accurate prediction of the likelihood of achieving adequate pain relief for patients with moderate to severe cancer within 2 weeks. Both of these tools, the EDSS and the CPPS, are important as well for prognostication of pain management outcomes.

The endpoint of the assessment of the patient is to establish a "pain diagnosis" and individualized pain treatment plan based on mutual agreement of goals.

The "pain diagnosis" should include the etiology and pathophysiology of pain:

- Etiology
  - Cancer
  - Cancer therapy (RT, chemotherapy, or surgery) or procedures
  - Not related to cancer

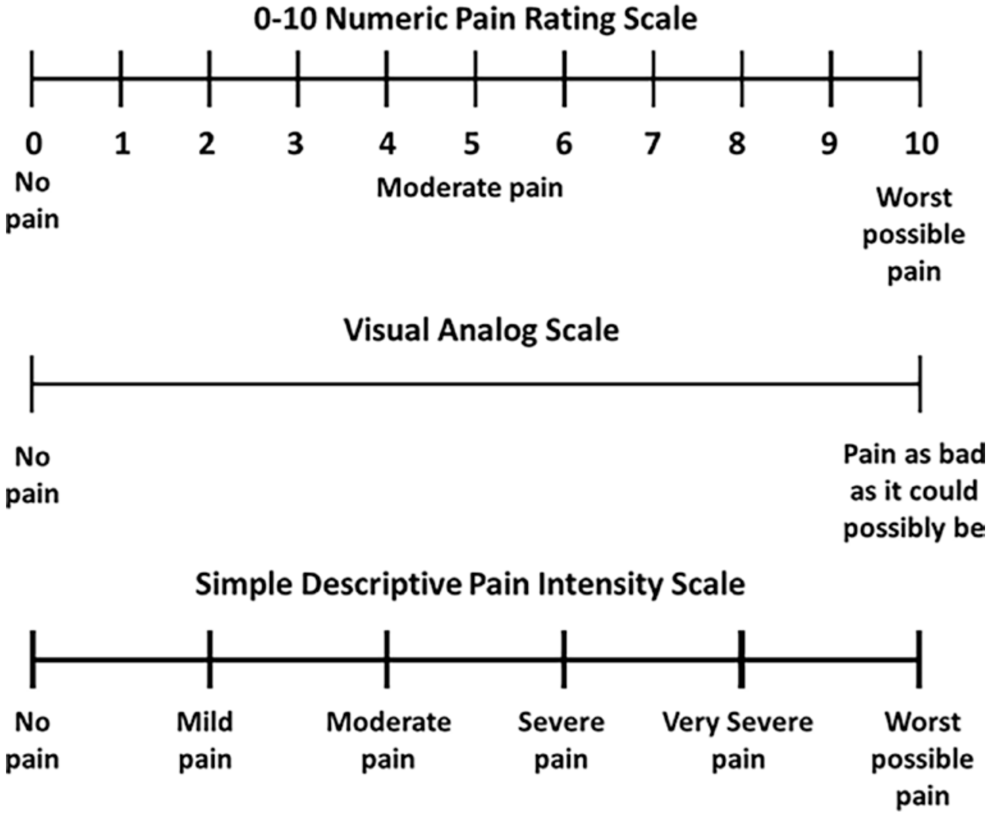
0-10 Numeric Pain Rating Scale
0
1
2
3
4
5
6
7
8
9
10
No pain
Moderate pain
Worst possible pain
Visual Analog Scale
No pain
Pain as bad as it could possibly be
Simple Descriptive Pain Intensity Scale
No pain
Mild pain
Moderate pain
Severe pain
Very Severe pain
Worst possible pain

Fig. 3 Different pain scales used to measure the pain intensity

- Pathophysiology
  - Nociceptive
  - Neuropathic
  - Mixed

5 Management of Cancer Pain

The management of cancer pain is often requiring a multidisciplinary approach. Radiotherapy, chemotherapy, hormones, bisphosphonates and surgery are all used to treat and palliate cancers and are directed against the etiology of pain. Most cancer pain management strategies will require [25]:

- A combination of pharmacologic and nonpharmacologic interventions
- Education of the patient, family and all caregivers about the plan
- Ongoing assessment of treatment outcomes.

To provide effective pain relief, the treatment must be customized to suit individual needs. Oncologists should have a working knowledge of pain management. The use of specific pharmacological agents and interventional techniques often require trained medical personnel who have clinical experience in managing cancer pain, which requires referral to specialty pain management centers.

Almost 45%–100% of cancer pain is relieved using an opioid-based analgesic regimen and using the WHO three-step analgesic ladder (Fig. 4) as guidelines [33].

The primary outcome of both the pain physician and the patient should be:

- To achieve a pain-free night
- To ensure pain-free at rest
- To improve a patient's activity of daily living with less discomfort and
- To control breakthrough incident pain (related to physical activity or movement) this is much more difficult to achieve.

Oral analgesic drug therapy is the mainstay for cancer pain management, which has been emphasized by guidelines issued by various organizations.

WHO analgesic ladder: Since 1986, the management of cancer pain had been based on the WHO 3-step analgesic ladder [34]. This simple guideline recommends oral analgesics which can be prescribed as per the severity of pain (mild, moderate, severe) from step one to three [35].

- For mild pain (generally 1 to 3 of 10 on a numerical rating scale), start at step 1.
- For moderate pain (generally 4 to 6 of 10), start at step 2.
- For severe pain (7 to 10 of 10), start at step 3.

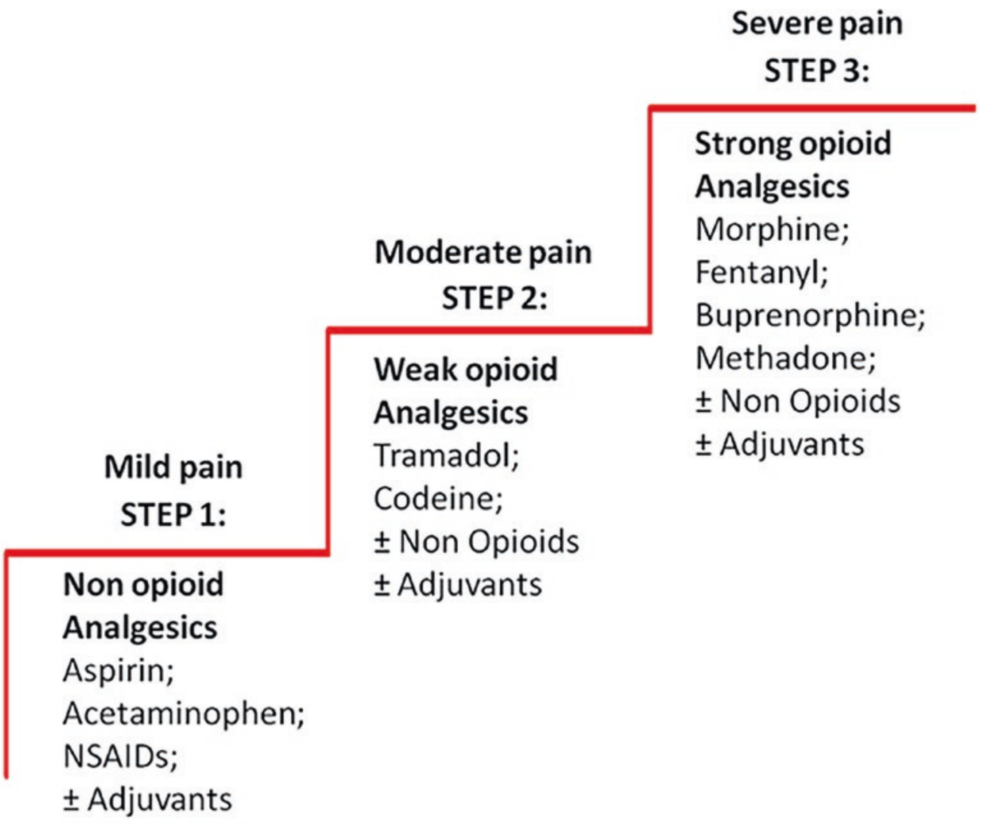
Severe pain
STEP 3:
Strong opioid Analgesics
Morphine;
Fentanyl;
Buprenorphine;
Methadone;
± Non Opioids
± Adjuvants
Moderate pain
STEP 2:
Weak opioid Analgesics
Tramadol;
Codeine;
± Non Opioids
± Adjuvants
Mild pain
STEP 1:
Non opioid Analgesics
Aspirin;
Acetaminophen;
NSAIDs;
± Adjuvants

Fig. 4 WHO three-step analgesic ladder

Analgesic potency gets escalated from nonopioid to weak-to-strong opioid-like oral morphine. Adjuvant drugs can be prescribed at any stage of the treatment.

The key principles include:

- **By the mouth**: Use oral analgesics whenever possible.
- **By the clock**: medications to be given on round the clock basis.
- **By the ladder**: escalate analgesics from nonopioid to weak opioid to strong opioid depending upon the pain severity and response.
- **For the individual:** Individualize the dose which provides a satisfactory pain relief with minimum side effects.
- **With attention to details**: monitoring adherence, side effects and adverse effects of the drugs prescribed.

The pharmacologic therapy includes the following:

- Nonopioid analgesics
- Opioid analgesics
- Adjuvant medications
- Anticancer therapy

6 Nonopioid Analgesics

Paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) are used for mild or moderate pain (Table 3). The efficacy of paracetamol and NSAIDs was concluded in a recent systematic, but there is equivocal evidence that the combination of the nonopioid and opioid is more effective than an opioid alone [36]. These drugs are most commonly used orally and their analgesia is limited by a ceiling effect. In patients with high gastrointestinal risk, selective cyclo-oxygenase-2 inhibitor, such as etoricoxib, or a nonselective inhibitor (diclofenac sodium) plus a proton-pump inhibitor, and in high cardiovascular risk, naproxen should be used; NSAIDs should not be used in the presence of both high gastrointestinal and cardiovascular risk [37]. NSAIDs provide effective pain relief in bone metastasis pain. Palliative Radiotherapy is the gold standard for bone pain but NSAIDs are adjuvants to further enhance the pain relief due to their anti-inflammatory mechanism. Combining NSAID to an opioid for severe cancer pain is efficacious, but the risk of long-term adverse effects has not been quantified. There is inadequate literature to support using acetaminophen with stronger opioids [38].

Table 3 Different types of available nonopioid analgesics

Name	Half-life (hours)	Dosing interval	Caution	Max doses (mg/day)
Acetaminophen	2–4	4–6	Hepatotoxicity	4000
Aspirin	3–12	4–6	GI toxicity, allergy, platelet inhibition	6000
Ibuprofen	3–4	4–8	GI and renal toxicity	4200
Naproxen sodium	12	12	GI and renal toxicity	1000
Ketoprofen	2–3	6–8	GI and renal toxicity	300
Indomethacin	4–5	8–12	GI and renal toxicity	150
Diclofenac	2–4	6	GI and renal toxicity	200
Ketorolac	4–6	4–6	GI and renal toxicity	300
Etoricoxib	6–8	12–24	Cardiovascular diseases	120

Table 4 Principles of opioid use

Choose a well-tolerated opioid
Use morphine as drug of choice for moderate to severe pain
Avoid opioids that are difficult to use, e.g., methadone, excess side effects, e.g., codeine
Use round-the-clock dosing
Identify indications for alternative or novel routes of administration
Quantity analgesic response and duration
Review opioid doses regularly until pain is controlled
Identify dose-limiting side effects
Anticipate constipation and psychological side effects
Diagnose opioid resistant pain syndromes
Be aware of the equianalgesic dose of opioids

Table 5 WHO step II opioids for moderate cancer pain in opioid-naive patients

Codeine	Use alone or in combination with paracetamol; doses ≥360 mg per day are not recommended
Tramadol	Use alone or in combination with paracetamol; doses ≥400 mg per day are not recommended

7 Opioid Analgesics

Opioid analgesics are mainstay in the management of cancer pain. During last two decades, there has been a dramatic increase in our knowledge of the sites and mechanism of action of opioids. In contrast to nonopioids, opioid analgesics (pure agonists) do not appear to have ceiling effect, i.e., as the dose is escalated, analgesia also increases and the increment in analgesic is linear to the point of loss of consciousness. Balancing the desirable (pain relief) and undesirable effects (nausea, vomiting, constipation, tolerance) is the challenge (Table 4). The selection of an opioid analgesic is based on the severity of pain needed to be treated based on the WHO three-step analgesic ladder.

Tramadol and codeine are used for treatment of moderate pain as in the WHO analgesic ladder step 2, while morphine, fentanyl, buprenorphine and methadone are used to treat severe pain as in step 3 of the WHO analgesic ladder.

Step II WHO analgesic ladder drugs should be added for inadequate pain control by paracetamol or NSAID (e.g., codeine or tramadol; Table 5) to achieve good pain relief without troublesome adverse effects. Alternatively, low doses of a step III opioid (e.g., morphine) may be used instead of codeine or tramadol. One randomized trial found that low-dose morphine (up to 30 mg daily) reduced pain significantly as compared to codeine (or tramadol) with or without acetaminophen in patients with moderate cancer pain with similar tolerability and an earlier effect [39].

Strong opioids (Table 6) are the mainstay of analgesic therapy in treating severe cancer pain. Clinically meaningful pain relief with tolerable side effects and an overall benefit to quality of life should be the goal of long-term opioid therapy [40].

Although the oral route of administration is advocated, the patients presenting with severe pain who need urgent relief should be treated and titrated with parenteral opioids, usually administered by intravenous (IV) route. If given parenterally, the equivalent dose is one-third of that of the oral medication.

Thus, if a patient in severe pain gets relief with 3 mg of IV morphine, the equianalgesic oral dose is 10 mg per dose and taking 4 h as half-life, the patient needs 60 mg of oral morphine in 24 h. When the pain relief is stable with the above therapy, this can be replaced either with sustained release morphine or transdermal preparations. The breakthrough dose is about the one-sixth or one-tenth 24-h morphine dose. Thus, if the patient needs 60 mg of morphine in 24 h, breakthrough dose will be 10 or 6 mg.

A change in the opioid drug or route of administration to improve therapeutic benefits and minimize harm and increase benefits is termed as opioid rotation or opioid switch.

When opioid requirements are stable, we can advise transdermal fentanyl and transdermal buprenorphine (Table 7). When patients are unable to swallow, patients with poor tolerance to morphine and patients with poor compliance, they are the treatment of choice.

Methadone has often been viewed as an alternative to oral morphine but its specific pharmacokinetic characteristics and a very long and unpredictable half-life [41] require careful individualization of dosing schedules.

The side effects of the opioid analgesics often limit their effective use. The most common side effects are:

- Nausea and vomiting: Use of antiemetic along with the opioid, or switching the opioids helps.
- Constipation: When opioid analgesics are prescribed, a regular bowel regimen including stool softeners with

Table 6 Mainstay strong opioids

Drug	Equianalgesic doses	Half-life	Duration of action (hrs)	Comments
Morphine	10 mg IM/IV/SQ; 20–30 mg PO	2–3 h; 2–3 h	3–4 h; 3–6 h	Standard for comparison for opioids; several routes available; cautious in renal failure
Codeine	200 mg PO	2–4 h	4–6 h	Used for moderate pain
Modified-release morphine	20–30 mg PO	2–3 h	8–12 h	–
Sustained-release morphine	20–30 mg	PO 2–3 h	12–24 h	–
Methadone	10 mg IM/IV/SQ, 20 mg PO	12– 150 h	6–8 h	Patients need increased vigilance for weeks, until steady state; can prolong the QTc interval, and ECG should be checked at doses higher than 100 mg per day
Fentanyl	50–100 μg IV/SQ	7–12 h	1–2 h	Can be administered as a continuous IV or SQ infusion
Fentanyl transdermal system	–	NA	48–72 h per patch	Refer to package insert for equianalgesic dosing guidelines for oral and parenteral medication; not usually recommended for opioid-naive patients in currently available doses; not recommended for acute pain
Transmucosal fentanyl citrate formulations	–	7–12 h	1–2 h	Indicated for the treatment of breakthrough pain

Table 7 Relative analgesic ratios for opioid switching

Opioid	Relative analgesic ratio	Strength of the recommendation for use
Oral morphine to TD buprenorphine[a]	75:1	Weak
Oral morphine to TD fentanyl[b]	100:1	Strong

TD Transdermal

[a] Example: 60 mg oral morphine to 35 μg/h TD buprenorphine (equivalent to 0·8 mg per 24 h)

[b] Example: 60 mg oral morphine to 25 μg/h TD fentanyl (equivalent to 0·6 mg per 24 h)

peristalsis enhancer should be started. Opioid antagonists (e.g., methyl naltrexone) that do not penetrate the blood-brain-barrier are new effective treatment for opioid-induced constipation.

- Sedation: Sedation and drowsiness vary with the drug and dose.
- Respiratory depression: Is rarely a problem because pain stimulates the respiratory center, and tolerance develops to this adverse effect.
- Multifocal myoclonus can occur and is treated by adding clonazepam. Dose reduction of opioid and opioid rotation also helps.

8 Adjuvant Drugs

These are commonly used to (1) provide analgesia for certain types of pain viz. neuropathic pain or somatic bone pain, (2) treat opioid side effects and (3) treat other symptoms associated with pain or to potentiate the analgesia of the drugs in a synergistic manner. These adjuvants are the integral part of WHO three stepladder guidelines, which can be used at any stage of the ladder.

The adjuvant analgesics [40] (Table 8) can be divided into (1) antidepressants, (2) anticonvulsants, (3) corticosteroids, (4) bisphosphonates, (5) anticholinergics and (6) somatostatin analogues.

Other adjuvant drugs such as clonidine, benzodiazepine, neuroleptics and NMDA antagonists (ketamine) are used in the management of neuropathic pain. Use of ketamine infusion has been found to be effective in certain cases of refractory neuropathic pain. The drugs, viz., bisphosphonates compound, radionucleotides, e.g., strontium 89, Samarium 153, have been found to effective in the treatment of pain with multifocal metastatic bone disease. Strontium 89 is indicated in patients with refractory multifocal pain due to osteoblastic lesion, who have a life expectancy greater than 3 months and have sufficient bone marrow reserves.

Table 8 Adjuvant analgesic agents in management of cancer pain

Adjuvants	Examples	Dose (mg)	Remarks
Antidepressants			
• TCA	Amitriptyline	10–25	Neuropathic pain
• SNRIs	Duloxetine	20–40	Better side effects profile than TCAs
• SSRIs	Escitalopram	10–20	Not much evidence
Anticonvulsants	Gabapentin Pregabalin	100–2600 75–600	Neuropathic pain, postsurgical pain
Steroids	Dexamethasone	2–8 mg per day, sometimes up to 20 mg per day	Bone pain, neuropathic pain, lymphedema pain, headache, bowel obstruction
Bisphosphonates	Zoledronate	4 mg every 3–4 weeks	Usually considered first-line treatment; also reduces other adverse skeletal-related events; concern about osteonecrosis of the jaw and renal insufficiency might restrict use
	Pamidronate,	60–90 mg every 2–3 weeks	
	Ibandronate	–	
Anticholinergics	Hyoscine compounds	–	In combination with steroids, used for bowel obstruction
Somatostatin analogues	Octreotide	0.3–0.6 mg per day	In combination with steroids, used for bowel obstruction

TCA Tricyclic antidepressants, *SSRI* Selective serotonin reuptake inhibitor, *SNRI* Selective noradrenaline reuptake inhibitor, *Mg* Milligram

9 Interventional Therapies

Interventional therapies, like nerve blocks, cementoplasty and other techniques, can be useful in the relief of cancer pain. Almost 10%–20% of patients with pain that is poorly responsive to opioids, or where there are intractable side-effects, may benefit from invasive procedures. It should be emphasized that such procedures are not the “fourth step” of the WHO analgesic ladder, but can and should be considered at each step depending on patient preference and need [42]. These procedures should be tried at an earlier stage to have maximal advantage and better quality of life. Intrathecal therapy by pump implant, neurolytic celiac plexus or superior hypogastric or ganglion impar block, spinal neurolysis, vertebroplasty and image-guided tumor ablation are some of the interventional procedures. About 8%–11% patients can benefit substantially from these procedures to reduce the side effects of analgesics. A temporary diagnostic block using a local anesthetic should always precede a neurolytic block. Some cancer pain syndromes are more amenable to neurolytic block, e.g., celiac plexus block for cancer pancreas and paravertebral somatic block for postthoracotomy pain syndrome.

9.1 Peripheral Blocks

9.1.1 Somatic Blocks

Peripheral nerves and plexus can be blocked in a similar manner to temporary perioperative block. Examples include brachial and lumbar plexus blocks. Intercostal blocks are often performed for chest wall pain, and give relief for an average of 3 weeks when phenol is used.

9.1.2 Visceral and Sympathetic Blocks

Visceral and sympathetic blocks are mainly used to control the pain originating from the viscera and sympathetic hyperactivity.

Celiac plexus block: used to relieve upper abdominal and referred back pain caused by malignancy involving the upper abdominal structure (pancreas, stomach, duodenum, liver and gall bladder).

Superior hypogastric plexus block: used to relieve pelvic pain due to malignancy of rectum, vagina, cervix and other pelvic organs.

Stellate ganglion block (cervicothoracic ganglion block): useful for pain in the face, upper neck and hemicranium.

Ganglion impar block: used to treat lower pelvic or perineal pain, coccydynia, troublesome tenesmus and anorectal pain from local malignancy.

9.2 Central Blocks

Intrathecal neurolysis may be used to provide long-lasting analgesia in malignant pelvic or perineal pain syndromes and may be helpful in severe chest or abdominal wall disease.

Phenol or alcohol can be used, with the hyperbaricity of phenol making it useful for perineal or pelvic pain, and the hypobaricity of alcohol lending itself to treatment in the cervical and thoracic levels [42].

9.3 Intrathecal Implantable Pumps

This is indicated when life expectancy is 3–6 months. The epidural or intrathecal catheter is tunneled and connected to an implanted pump which sits in the superolateral quadrant of the buttock or the anterior abdominal wall. Morphine (somatic pain) or Ziconotide are the drugs commonly used through this therapy.

Radiofrequency denervation, spinal cord stimulation and dorsal column stimulation (DCS) have also been successfully used in selected cases.

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Intensive Care

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Abbreviations

AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ASPEN	American Society for Parenteral and Enteral Nutrition
BIA	Bioimpedance analysis
BMT	Bone marrow transplant
BSA	Body surface area
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DAH	Diffuse alveolar hemorrhage
DEXA	Dual X-ray absorptiometry
ECMO	Extra corporeal membranous oxygenation
EOLC	End-of-life care
HFNC	High flow nasal cannula
HLH	Hemophagocytic lymphohistiocytosis
ICP	Intracranial pressures
ICU	Intensive care unit
MDR	Multidrug-resistant
MNA	Mini nutritional assessment
MST	Malnutrition screening tool
MUST	Malnutrition universal screening tool
PCR	Polymerase chain reaction
SAPS	Simplified acute physiology score
SIADH	Syndrome of inadequate antidiuretic hormone secretion
SOFA	Sequential organ failure assessment score
SVC	Superior vena cava
TLS	Tumor lysis syndrome
TRALI	Transfusion-associated acute lung injury
WHO	World Health Organization

1 Introduction

Critically ill oncology patients have distinct physiologic and pathological characteristics specific to cancer that set them apart from other critically ill patients [1, 2]. They are prone to cancer-specific complications such as drug toxicities and tumor lysis, and are also at a higher risk to develop overwhelming sepsis, opportunistic infections and multi-organ dysfunction due to cancer or cancer treatments. For a positive outcome in oncology critical care, the treating doctors should have a thorough knowledge about the current illness and disease process, along with an understanding of oncology-specific issues [2]. This familiarity about the pathophysiology of various diseases and the host response to disease states, result in better care to the patient [3]. Oncology critical care is no longer considered as futile and currently plays an important role in planning treatment options, including aggressive chemotherapies and aggressive surgeries to an otherwise vulnerable population [4]. The intensive care unit (ICU) currently admits extremely vulnerable patients and yet is able to maintain good quality of life in approximately 50% of all these patients after ICU discharge [4]. This is in large measure due to the advances that have incurred in the area of critical care (Table 1). Apart from usual challenges in the ICU, the oncology critical care is challenging due to few cancer-specific complications as enlisted in Table 2.

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Table 1 Changes that incurred in oncology critical care over years

Increase in the number of patients being admitted to ICU for oncology-specific critical care.
Increased administration of chemotherapeutic agents in ICU for oncologic emergencies.
Significant change in practice from invasive ventilation to noninvasive strategies such as noninvasive ventilation (NIV) and high flow oxygen by nasal cannula (HFNC).
Availability of better therapeutic agents and treatment strategies, e.g., newer antimicrobial agents, chemotherapeutic agents.
A significant increase in ICU survival and improved quality of life after ICU discharge.

Table 2 Challenges pertinent to oncology critical care

Patients are highly prone to otherwise rare medical emergencies due to a variation form normal immunity, physiology and anatomy such as opportunistic infections, difficult airway, etc.
There is a high incidence of oncologic emergencies such as tumor lysis syndrome (TLS), airway emergencies, metabolic emergencies, neuroemergencies and circulatory complications that require urgent intervention and management.
Specific treatment-related complications such as life-threatening capillary leakage, hypotension and acute respiratory distress are seen in patients receiving chimeric antigen receptor modified T cells (CART), chemotherapy induced pneumonitis and chemotherapy induced organ damage.
Increased incidence of postoperative complications due to extensive and radical surgeries.

2 Integrated Approach to Oncologic Critical Care

In the ICU, most of the critically ill oncology patients will have multiple comorbidities apart from cancer-specific problems. Therefore, the inputs regarding patient management should be taken from the treating physician (oncologist or oncosurgeon), intensivist and other departments including rehabilitation therapy, nutrition, pain services, palliative care services, etc. [5]. This integrative care should start from the initial hospital visit itself, preferably before any ICU admission. The patient should be evaluated in detail, and the expected course of the disease, the treatment options and expected outcome should be conveyed to the patients and relatives in an empathetic yet realistic manner. After initiation of cancer directed treatment, the response of the disease to the treatment must be evaluated periodically. All further treatment plans should to be formulated based on the treatment response, the symptom relief obtained, the nutritional status, performance score and the necessity of providing further symptom management and comfort care.

When the need for intensive care is anticipated or arises, the parent unit should initiate a discussion with the intensive care team and also with the patient and patient relatives. All patients who are expected to benefit from intensive care may be shifted to the ICU if they are willing for the same. During the stay in ICU, the patient's progress should be assessed daily by the team who has already evaluated the patient. Concerns regarding the patient's treatment and progress should be discussed collectively among the treating team. Several patients admitted to ICU will receive full code management for the initial 3–5 days as a part of a time bound ICU treatment trial [6]. Once the patient improves and no longer requires ICU support, they may be shifted back to the wards in conjunction with the primary team. These patients need to be followed up for identifying and treating complications related to ICU stay including post intensive care syndrome. Figure 1 summarizes a flowchart of integrating care from initial hospital visit to post ICU discharge.

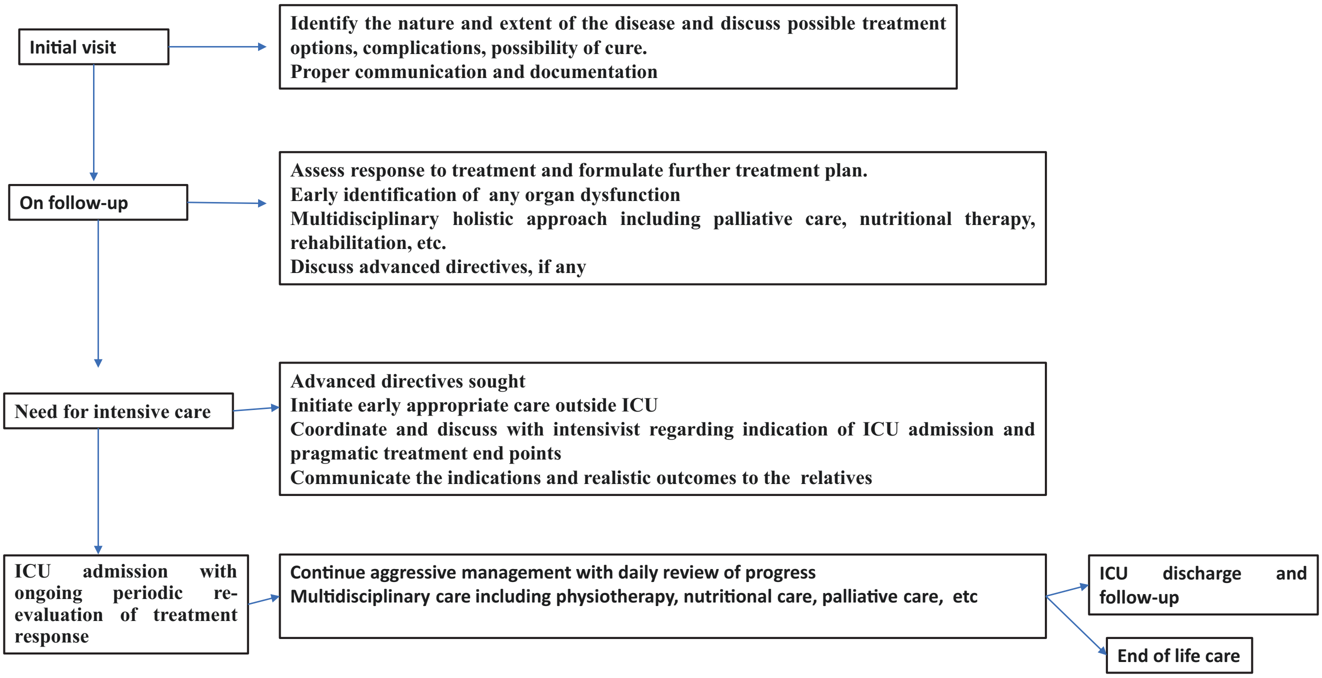
Initial visit
Identify the nature and extent of the disease and discuss possible treatment options, complications, possibility of cure.
Proper communication and documentation
On follow-up
Assess response to treatment and formulate further treatment plan.
Early identification of any organ dysfunction
Multidisciplinary holistic approach including palliative care, nutritional therapy, rehabilitation, etc.
Discuss advanced directives, if any
Need for intensive care
Advanced directives sought
Initiate early appropriate care outside ICU
Coordinate and discuss with intensivist regarding indication of ICU admission and pragmatic treatment end points
Communicate the indications and realistic outcomes to the relatives
ICU admission with ongoing periodic re-evaluation of treatment response
Continue aggressive management with daily review of progress
Multidisciplinary care including physiotherapy, nutritional care, palliative care, etc
ICU discharge and follow-up
End of life care

Fig. 1 Flowchart summarizing the integrated pattern of care in oncology critical care

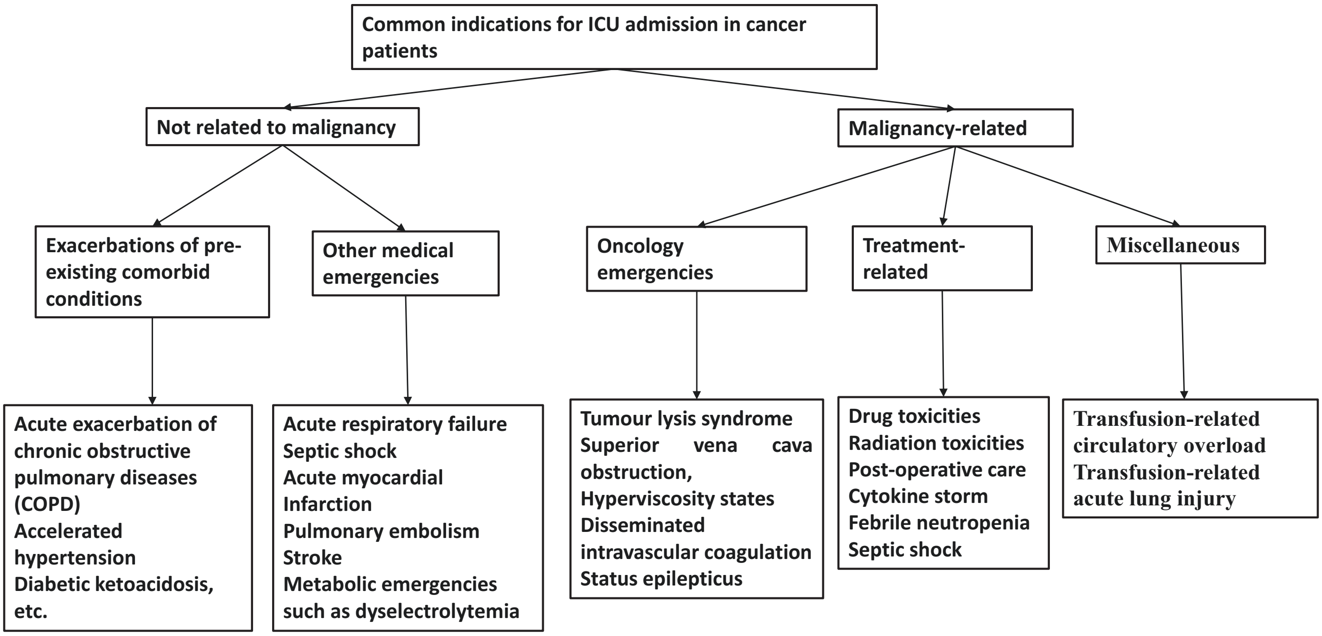
Common indications for ICU admission in cancer patients
Not related to malignancy
Malignancy-related
Exacerbations of pre-existing comorbid conditions
Other medical emergencies
Oncology emergencies
Treatment-related
Miscellaneous
Acute exacerbation of chronic obstructive pulmonary diseases (COPD)
Accelerated hypertension
Diabetic ketoacidosis, etc.
Acute respiratory failure
Septic shock
Acute myocardial Infarction
Pulmonary embolism
Stroke
Metabolic emergencies such as dyselectrolytemia
Tumour lysis syndrome
Superior vena cava obstruction,
Hyperviscosity states
Disseminated intravascular coagulation
Status epilepticus
Drug toxicities
Radiation toxicities
Post-operative care
Cytokine storm
Febrile neutropenia
Septic shock
Transfusion-related circulatory overload
Transfusion-related acute lung injury

Fig. 2 Common indications for admission in oncology critical care units

3 Admission into Oncology Critical Care Units

Patients will require intensive care for diseases related to or unrelated to the natural course of the underlying malignancy [7] (Fig. 2). Neither clinical judgment nor screening tools can accurately identify the subset of patients who may benefit from ICU care [8–10]. Hence, the policies for admitting oncology patients into critical care units have to be designed locally and are described in Table 3.

The ICU admission policies should be based on the principles of beneficence, nonmaleficence, autonomy and justice [1]. At times, patients are required to be admitted for a time bound trial of ICU care to avoid delay in ICU admis-

Table 3 Admission patterns followed in oncology critical care

Admission type	Implication	Indication
Full code	For full aggressive treatment including all invasive procedures until the disease resolves	Patients in whom complete recovery and a good ICU free survival is anticipated. For example, those with their disease states cured from malignancy, postoperative patients, and those who are treatment naïve—newly diagnosed malignancy with unknown treatment response, etc.
ICU trial	For full aggressive treatment including all invasive procedures for a prespecified time after which the response to treatment is evaluated and further plan is made	Patients in whom the therapeutic response to treatment is uncertain, those who are treatment naïve or those in the initial phases of treatment. Aggressive treatment is provided for 3–5 days and then the patient is re-evaluated and decisions regarding further treatment are made according to the response to the treatment given so far.
Limited ICU Trial	ICU admission with clear instructions regarding management including the treatments to be offered and withheld.	Patients are admitted to ICU for treatments that cannot be provided in ward (e.g., noninvasive ventilation) or those requiring frequent monitoring (pain management after a palliative procedure)
Exceptional ICU admission	ICU admission for the management of otherwise acute and reversible causes	Patients who develop acute illness that is potentially reversible with minimal interventions and care. For example, dyselectrolytemia, glycemic emergencies, etc.
Prophylactic admission	ICU admission for patients who are currently stable but expected to have a rapid deterioration And a narrow therapeutic window between deterioration and clinical management.	Admission for those who are anticipated for tumor lysis syndrome (TLS) anticipated tumor bleeding or in who severe reactions to treatment is anticipated (e.g., CART therapy—see text)
Miscellaneous	ICU admissions not fitting in above criteria	Patients admitted to ICU due to a lack of consensus regarding advanced directives between the intensivist/primary physician/relatives
NO admission	Patients who are unlikely to benefit from ICU admission are often denied admission to ICU.	Patients admitted with advanced malignancy, those who have failed on all possible treatment regimes, moribund patients, etc.

sion. This is also important as a delay in ICU admission is associated with increased mortality. During the ICU stay, while continuing treatment they may be evaluated for treatment response or treatment futility [6] Patients who fail to benefit from the ICU trial or those who further deteriorate despite maximal aggressive medical therapy should be identified early and should be considered for nonescalation of further treatment after detailed discussion between the treating teams of physicians initially and later with the family.

Patients who are predicted not to benefit even from the best supportive care—e.g., those with end-stage disease conditions or those with reduced life expectancy or those with pre-existing poor performance scores—may be denied ICU care and instead shifted to a palliative care setting [4].

4 Management of Critically Ill Oncology Patient Admitted to an ICU

The management of common medical emergencies unrelated to malignancy remains unchanged regardless of the presence or absence of malignancy, e.g., management of myocardial infarction, cardiac failure, acute exacerbation of chronic obstructive pulmonary disease (COPD), etc. Description of the management of these common diseases is out of the scope of this chapter and will not be considered here.

5 Management of Oncologic Emergencies

Oncologic emergencies (metabolic or nonmetabolic) are the leading cause of ICU admission in centers catering to oncology patents. A brief description of the initial management of these is given below.

5.1 Respiratory Failure

Acute respiratory failure (ARF) is the one of the leading cause of ICU admissions for oncology patients. Among patients with hematologic and solid malignancies, approximately 5%–50% of ICU admissions are due to respiratory failure while about 42%–88% of ICU admissions in hematopoietic stem cell transplant recipients are due to respiratory failure. Infections, pulmonary edema, radiation induced lung damage/chemotherapy induced pneumonitis, diffuse alveolar hemorrhage (DAH), pulmonary embolism, disease progression causing respiratory failure, etc. are the common causes of ARF resulting in ICU admission [11].

Majority of the pulmonary infections are due to common bacteria, although opportunistic infections like pulmonary aspergillosis, pneumocystis jirovecii pneumonia, mucormycosis, respiratory viral infection including cytomegalovirus, etc. are also common. Many of these infections eventually progress to acute respiratory distress syndrome (ARDS).

Noninfectious causes of respiratory failure include sepsis, drug induced lung injury, transfusion-associated acute lung injury (TRALI), pulmonary alveolar proteinosis, bronchiolitis obliterans and organizing pneumonia, hemophagocytic lymphohistiocytosis and rarely due to progression of underlying malignancy (Lymphangitis carcinomatosis or pulmonary leukostasis/leukemic infiltration).

5.1.1 Management of Acute Respiratory Distress Syndrome

Management of acute respiratory failure includes a complex multimodal diagnostic approach, i.e., a clinicoradiological approach assisted by microbiological investigations such as staining, culture, or polymerase chain reaction (PCR) of a lower respiratory tract specimen or lung biopsies, galactomannan assays, etc. [12].

An example of multimodal approach for acute respiratory failure is shown in Fig. 3 [13]. This approach has aided to reduce the mortality rates from 89% to approximately 59%, 63% and 68.5%, respectively, in mild, moderate and severe ARDS [14, 15]. The initial high mortality for ARDS was considered to be the complications of invasive ventilation, and noninvasive ventilation (NIV) was suggested as a tool to tide over the same. However, as the management strategies of invasive ventilation in ARDS improved, the initial enthusiasm for NIV gradually reduced. The overall NIV failure rates are as high as 70%, especially in severely ill patients. Early administration of NIV has not been shown to improve mortality rates in patients with high SOFA score, severe ARDS or associated pulmonary infections [16]. High flow nasal cannula (HFNC) can deliver humidified oxygen at very high flow rates—even up to 60 L/min. These high flow rates help to maintain a positive end-expiratory pressure, aid in alveolar recruitment, improve oxygenation and reduce the work of breathing. Trials have showed a trend toward mortality benefit in Type I respiratory failure patients among immunosuppressed patients and cancer patients when treated with HFNC as compared to NIV [17, 18]. However, these require further validation by adequately powered good quality trials [5, 6]. Extracorporeal membranous oxygenation (ECMO) for ARDS in malignancy requires expertise due to complications such as bleeding and infections [19]. ECMO may thus be considered only in selected group of patients, and in centers with adequate experience in dealing with both ECMO and oncology patients.

5.2 Sepsis

Oncology patients are usually immunosuppressed due to the underlying malignancy or due to an iatrogenic neutropenia (absolute neutrophil count <1500/cc). These patients are prone to overwhelming infection with common pathogens as well as opportunistic pathogens. Severe infections are seen in those with profound neutropenia (absolute count of PMN less than 100) or if the duration of neutropenia extends more than 7 days. International societies have published guidelines of management of febrile neutropenia in ICU and also

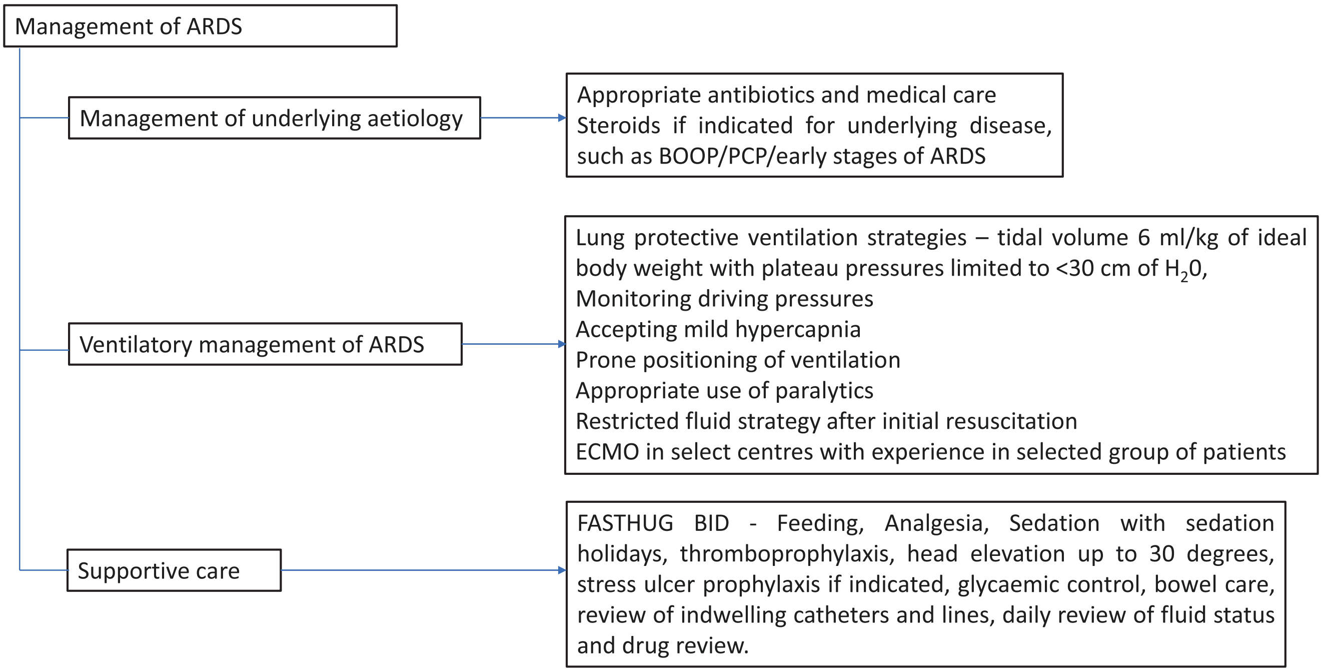
Management of ARDS
Management of underlying aetiology
Appropriate antibiotics and medical care
Steroids if indicated for underlying disease, such as BOOP/PCP/early stages of ARDS
Ventilatory management of ARDS
Lung protective ventilation strategies – tidal volume 6 ml/kg of ideal body weight with plateau pressures limited to <30 cm of H_20,
Monitoring driving pressures
Accepting mild hypercapnia
Prone positioning of ventilation
Appropriate use of paralytics
Restricted fluid strategy after initial resuscitation
ECMO in select centres with experience in selected group of patients
Supportive care
FASTHUG BID - Feeding, Analgesia, Sedation with sedation holidays, thromboprophylaxis, head elevation up to 30 degrees, stress ulcer prophylaxis if indicated, glycaemic control, bowel care, review of indwelling catheters and lines, daily review of fluid status and drug review.

Fig. 3 Management of ARDS

regarding outpatient management of febrile neutropenia [20–22]. Empirical antibiotic treatment for multidrug-resistant (MDR) pathogens will be required for majority of these patients. In patients with hemodynamic instability, additional coverage for gram-positive pathogens and fungal pathogens might also be required.

The pathophysiology of sepsis and septic shock remains the same as in those without cancer. No clinically significant differences have been demonstrated in the macro circulation or the microcirculation. Due to a dysregulated host response to infection, multiorgan dysfunction sets in and multiorgan dysfunction is associated with a worse prognosis than neutropenia or disease progression. The host response to infection is often blunted, preventing early recognition, and patients present with signs and symptoms of infections of the lungs, GI tract, urinary tract or at times as primary bacteremia with source unidentified.

5.2.1 Management of Sepsis in ICU

The management of sepsis in oncology patients is similar to those without malignancy (Fig. 4). It is to be considered as a medical emergency, needs to be identified early and managed with hydration (30 mL/kg crystalloids), ongoing hemodynamic evaluation, hemodynamic support (including management of fluid responsiveness), antibiotics, vasopressors and appropriate source control wherever feasible [23]. In cases of life-threatening emergencies, the presence or suspicion of sepsis or requirement of life support systems should not defer the administration of chemotherapy if otherwise indicated [24]. With the implementation of sepsis bundles, the mortality rate of sepsis has reduced to 40% in oncology patients. Antibiotics should be selected as per the foci of infection, prior antibiotics received, prevailing local antibiogram, possibilities of opportunistic and fungal infections, underlying disease characteristics and pharmacokinetic–pharmacodynamic principles. They should be administered early, after appropriate cultures are sent. The antibiotic therapy may be deescalated later once culture reports are available or if there is a positive treatment response.

In patients with septic shock or organ dysfunction, treatment should be initiated with a broad-spectrum agent such as carbapenem. Polymyxins like colistin and polymyxin B also may be required, as per the available local antibiogram, case history and renal function. Combination therapy with a third or fourth-generation cephalosporin and aminoglycoside or meropenem and a polymyxin may also be used if aerobic gram negative infections are suspected. Coverage for gram-positive organisms needs to be added in patients with hemodynamic instability or as per international guidelines /local institute treatment protocols [21]. Neutropenia, diabetes mellitus, chronic renal failure, indwelling catheters prolonged antibiotics therapy multisite fungal infection or colonization, etc. are considered high risk for invasive fungal infection. Antifungal agents need to be added empirically to such patients and also to patients who fail to improve even after initial appropriate antibiotic therapy. In hemodynamically unstable patients, echinocandins preferred for antifungal therapy. Liposomal amphotericin B is a second-line drug for escalation or used as an initial therapy if the patients were already receiving posaconazole or voriconazole [25].

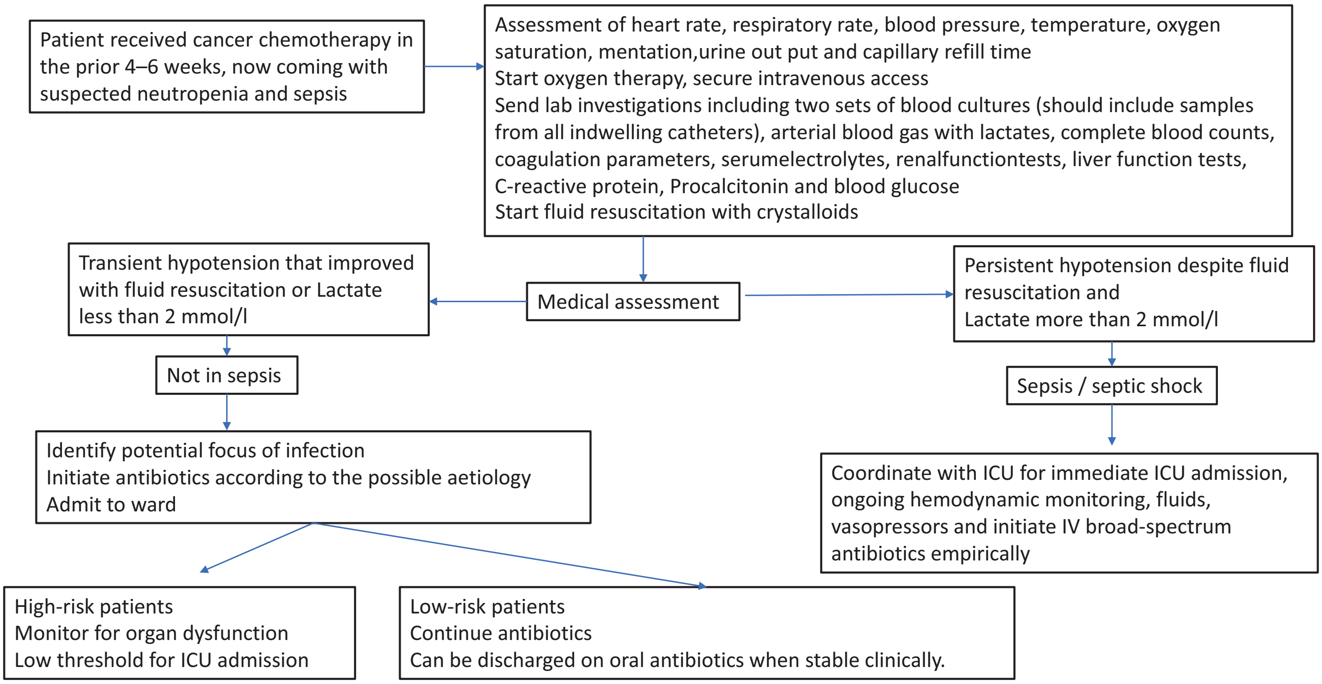
Patient received cancer chemotherapy in the prior 4–6 weeks, now coming with suspected neutropenia and sepsis
Assessment of heart rate, respiratory rate, blood pressure, temperature, oxygen saturation, mentation,urine out put and capillary refill time
Start oxygen therapy, secure intravenous access
Send lab investigations including two sets of blood cultures (should include samples from all indwelling catheters), arterial blood gas with lactates, complete blood counts, coagulation parameters, serumelectrolytes, renalfunctiontests, liver function tests, C-reactive protein, Procalcitonin and blood glucose
Start fluid resuscitation with crystalloids
Medical assessment
Transient hypotension that improved with fluid resuscitation or Lactate less than 2 mmol/l
Not in sepsis
Identify potential focus of infection
Initiate antibiotics according to the possible aetiology
Admit to ward
High-risk patients
Monitor for organ dysfunction
Low threshold for ICU admission
Low-risk patients
Continue antibiotics
Can be discharged on oral antibiotics when stable clinically.
Persistent hypotension despite fluid resuscitation and
Lactate more than 2 mmol/l
Sepsis / septic shock
Coordinate with ICU for immediate ICU admission, ongoing hemodynamic monitoring, fluids, vasopressors and initiate IV broad-spectrum antibiotics empirically

Fig. 4 Initial assessment and management of sepsis in oncology critical care

5.3 Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome (TLS) is an acute life-threatening emergency in patients with large tumor load, e.g., Burkitt's lymphoma, acute leukemia and rarely a solid tumor.

Tumor lysis may occur spontaneously in rapidly proliferating malignant cells; more commonly, once treatment is initiated, massive cell lysis occurs, releasing large amounts of intracellular phosphorous and potassium into the circulation. Their serum levels increase to dangerously high values and can predispose to life-threatening cardiac arrhythmias. There is also increased release and break down of nucleic acids leading to hyperuricemia which can cause urate nephropathy, cardiac conduction defects and gout. Calcium binds with circulating phosphate resulting in calcium phosphate crystallization in the kidneys and further worsens renal failure and urate nephropathy [26].

5.3.1 Management of Tumor Lysis Syndrome

TLS is managed by early identification, prophylactic administration of uricosuric agents, phosphate binders and potassium binders. Hydration is started at a rate of 200 mL/kg/day or 2 to 3 L/m^2 of body surface area (BSA) to maintain a urine output of 100 mL/m^2 BSA in high-risk cases. Dialysis may be required in case of life-threatening hyperkalemia or hyperphosphatemia not controlled with medical management (either due to increased production or a decrease in the kidney function), presence of fluid overload, or in cases where underlying comorbid conditions restrict the intake of fluids [26]. Pathophysiology and management of tumor lysis syndrome is described in Fig. 5.

5.4 Dyselectrolytemia

Apart from TLS, patients with malignancy present to ICU with acute dyselectrolytemia including hypercalcemia, hyponatremia, etc. Hypercalcemia occurs in approximately 10%–20% of cancer patients and presents with nonspecific neurological symptoms like confusion, nausea, constipation, lethargy, etc. It is important to identify these complications as it can rapidly progress to coma and death. Hypercalcemia is managed by aggressive rehydration, calcitonin followed by intravenous bisphosphonates, steroids in case of granulomatous disease or rarely dialysis for refractory hypercalcemia.

Symptomatic hyponatremia commonly occurs due to syndrome of inadequate antidiuretic hormone secretion (SIADH), hypovolemia, inadequate oral intake or underlying cardiac or liver dysfunction. Acute symptomatic hyponatremia can also occur due to rapid urinary sodium lose, especially after chemotherapy with cyclophosphamide, cisplatin, etc. Acute hyponatremia is a medical emergency due to acute onset rapid cerebral edema. Hence, for all patients with symptomatic hyponatremia, 2–4 mL/kg of 3% saline should be given as a rapid bolus over 20 min. The dose may be repeated if the patient remains symptomatic and the rise in serum sodium is less than 8–10 mmol/day. Caution should be taken to avoid rapid correction of serum sodium (more

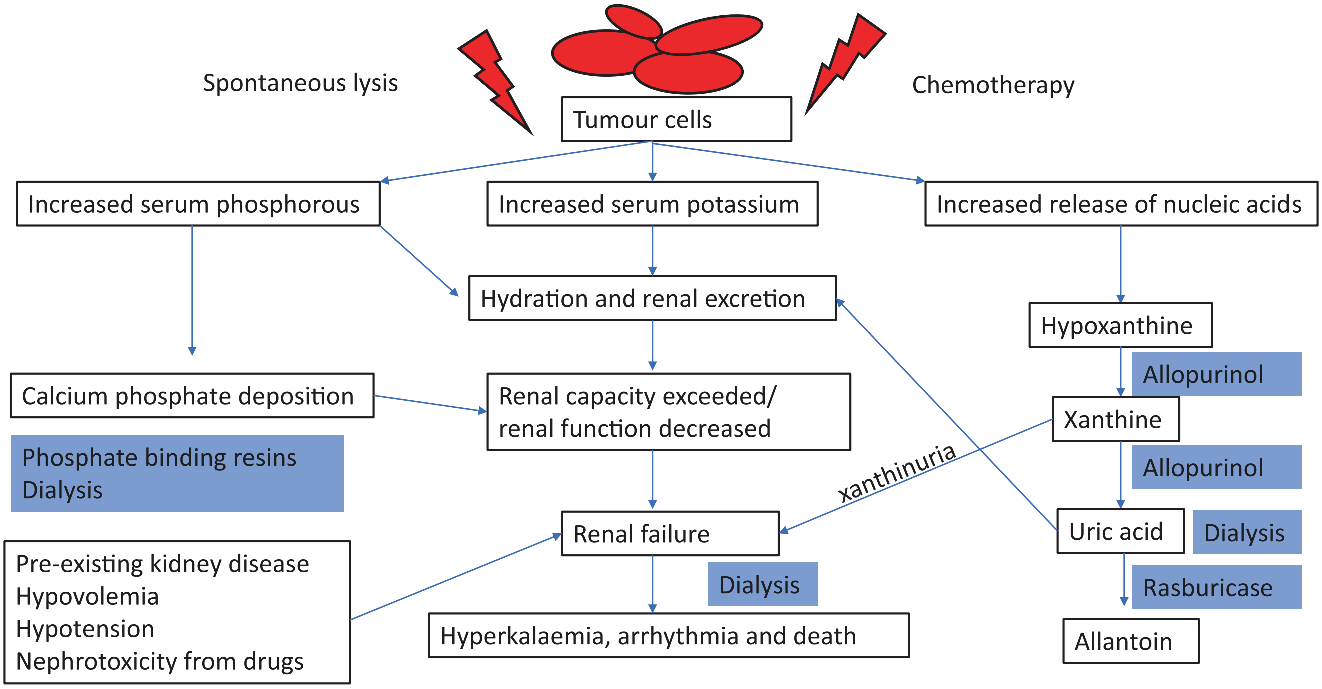
Spontaneous lysis
Chemotherapy
Tumour cells
Increased serum phosphorous
Increased serum potassium
Increased release of nucleic acids
Hydration and renal excretion
Hypoxanthine
Allopurinol
Calcium phosphate deposition
Renal capacity exceeded/
renal function decreased
Xanthine
Phosphate binding resins
Dialysis
Allopurinol
xanthinuria
Renal failure
Uric acid
Dialysis
Pre-existing kidney disease
Hypovolemia
Hypotension
Nephrotoxicity from drugs
Dialysis
Rasburicase
Hyperkalaemia, arrhythmia and death
Allantoin

Fig. 5 Pathophysiology and management of tumor lysis syndrome

than 8–10 mmol/day), as rapid corrections may result in osmotic demyelination syndromes [27, 28].

5.5 Airway Emergencies

Compromise of the airway can occur due to the local spread of the disease or secondary to mediastinal compression of the superior vena cava (SVC syndrome). Patients present with respiratory distress, hemoptysis, cough, etc. and may have audible stridor. Evaluation of the cause of airway compromise should comprise of a computerized tomography scan as it may aid in differentiating the causes of acute dyspnea, and helps to formulate a treatment plan by predicting the possible complications during intubation. Direct visualization of the airway by rigid or flexible bronchoscopy can also be attempted as it may serve both as a diagnostic and therapeutic tool. Management in such cases requires interventions to secure the airway including intubation if needed and definitive management of the local cause by radiation, or chemotherapy depending upon the nature of malignancy. In the case of thymic tumors, respiratory distress can be due to a direct tracheal compression well as due to myasthenia. In such cases, thymectomy can relieve the airway compression and cure myasthenia in a subset of patients [29]. Involvement of the tracheal or bronchial lumen by tumor may necessitate tracheobronchial stenting or debulking. This will need an expert multidisciplinary team of pulmonologists, thoracic surgeons and anesthesiologists for best outcomes.

5.6 Cardiac Dysfunction

Cardiac dysfunction can result from the direct involvement of cancer on the heart, pericardium and great vessels or due to the cardiotoxicity of the medicines used in cancer treatment. Anthracyclines like doxorubicin, monoclonal antibodies like trastuzumab, etc. are well known for their cardiac side effect profile. Patients develop arrhythmias or new ECG changes such as QTc prolongation, and present with breathlessness, or cardiogenic shock. Radiation-associated cardiotoxicity usually present with coronary artery disease, valvular dysfunction, dilated cardiomyopathy, conduction defects and diastolic heart failure. Radiation pericarditis occurs acutely on starting treatment or may present as late as 6 months to 1 year after treatment. Medications such as Dasatinib or surgical procedures such as pneumonectomy can cause pulmonary hypertension (PH) and right heart failure. Cardiac tamponade can be caused by massive pericardial effusions. The patients present with chest pain, light headedness, palpitations, dyspnea, orthopnea and dry cough. Bedside echocardiography will reveal collapse of right sided cardiac chambers during diastole. Cardiac failure and pulmonary hypertension are managed in same way as that of noncancer patients with noninvasive ventilation, diuretics, vasodilators and inotropes. Management of pericarditis or tamponade according to the etiology at times needs surgical interventions such as draining a tamponade or pericardiotomy [30, 31].

5.7 Acute Abdomen

Abdominal malignancies can present as subacute intestinal obstruction, intestinal obstruction, or at times as a surgical emergency due to bowel perforation and peritonitis. Infiltration or obstruction of the gall bladder or biliary tract by tumor can cause biliary obstruction, cholangitis and jaundice. Tumour infiltration into major vessels may cause massive hemorrhage and present as hemorrhagic shock. Obstruction to the urinary outflow at the level of the ureters or bladder can cause hydroureteronephrosis, acute kidney injury, acidosis and hypercalcemia. Patients who have received radiation to the pelvis can present later with radiation induced strictures of ureters causing post renal acute kidney injury (AKI), metabolic acidosis and pulmonary edema. The management of acute abdomen requires a case based multimodal approach involving the surgeons, intensivists, interventional radiologists and other specialties including nephrologists for dialysis as per the situation [32].

5.8 Emergencies of the Central Nervous System

Malignancy of the central nervous system (primary and secondary) can present with signs of raised intra cranial pressure such as altered sensorium or seizures. This is a medical emergency and often requires urgent surgical decompression along with medical management. Temporary measures to reduce the intra cranial pressure include anti epileptics, osmotherapy with mannitol or hypertonic saline, administration of corticosteroids, intubation, sedation and paralysis while maintaining normothermia, normoxia and normoglycemia, and avoiding hyper- or hypocarbia.

Acute onset paraplegia may result from epidural or bony metastasis causing spinal cord compression from primaries in lung, breast, prostate, etc. or in cases of multiple myeloma, lymphoma, etc. Patients usually present with symptoms such as pain, motor weakness, sensory symptoms, bowel and bladder involvement, etc. Early suspicion, diagnosis and immediate administration of glucocorticoids, surgery, radiotherapy and systemic chemotherapy in patients with chemosensitive tumors are important to prevent permanent nerve damage.

These patients are also at high risk of other CNS emergencies such as status epilepticus, venous sinus thrombosis, ischemic stroke, cerebral hemorrhage, etc. Management includes prompt diagnosis of the etiology and early treatment [33].

5.9 Adrenal Crisis or Adrenal Insufficiency

Acute adrenal insufficiency can occur due to the replacement of the glandular tissue by neoplastic tissue, due to surgical excision of both glands or at times due to hemorrhage into the adrenals in severe sepsis. Clinical features include nausea vomiting, diarrhea, vague abdominal or flank pain, confusion and vasopressor-resistant hypotension. A high degree of suspicion and supplementation with daily physiologic doses of glucocorticoids after confirming the diagnosis is the main stay of management [34].

6 Postoperative Care in Oncology

Surgeries in oncology patients are most often complex surgeries that involve extensive tissue dissection resulting in fluid shifts and third space loss, electrolyte imbalance, cardiac arrhythmias, impaired glucose control, hypothermia, etc. During the postoperative period, these patients are prone to complications such as bleeding, respiratory failure, malnutrition, venous thrombosis, etc. These patients require more aggressive postoperative monitoring apart from the routine postoperative care such as care till complete recovery from anesthesia, optimizing pain medications and complications such as shivering or postoperative nausea and vomiting [7].

7 Chemotherapy in ICU

Chemotherapeutic agents are extremely toxic drugs requiring specialized knowledge in preparing and administering the drugs. These drugs are now increasingly being used in the ICU to treat or prevent life-threatening malignancy-related emergencies such as hyperleukocytosis, hemophagocytic lymphohistiocytosis (HLH), tumor lysis syndrome, etc. The ICU team should be cautious while administering chemotherapeutic agents and the recommendations regarding dilution, volume, infusion rate, etc. should be followed. In case of any drug reactions, drug toxicities, or drug extravasations, the drug infusion should be stopped immediately and help from oncohematology should be sought [24].

8 Infection Control in ICU

Nosocomial infection commonly affects oncology patients due to their immunosuppression and the rates can be as high as 40%. These carry a huge implication in terms of cost of treatment, morbidity, mortality and length of stay in ICU and hospital. Hence, a systematic approach to reduce these infections is required. Simple measures like maintaining hand hygiene have been proved to be effective in reducing infection rates in hospital. All hospitals now adhere to the "five moments of hand washing" as suggested by World Health Organization (WHO) [35]. Apart from hand hygiene, many bundles (evidence-based group of interventions, each with a high grade of evidence in itself, when performed together adds on to produce a cumulative benefit) have been devised to reduce hospital acquired infections. These infection control bundles are summarized in Table 4 [36, 37].

Table 4 Common bundles in ICU for infection control [35–37]

Ventilator-associated pneumonia bundle	Head end elevation of bed Daily interruption of sedation and spontaneous breathing trials Aspiration of subglottic secretions Peptic ulcer prophylaxis in high-risk patients Deep vein thrombosis prophylaxis
Catheter-related blood stream infections bundle	Maintaining good hand hygiene practices Strict aseptic precautions during line insertion Use of chlorhexidine for skin antisepsis Preference of subclavian and jugular sites over femoral sites Daily review of indwelling catheters and prompt removal of unnecessary lines
Catheter-associated urinary tract infection bundle	Avoid unnecessary urinary catheterizations Catheterize in aseptic precautions Daily care of urinary catheter and remove if not required.

9 Nutrition in Oncology Critical Care

Most of the cancer patients will be malnourished due to reduced oral intake and cachexia of malignancy and complications of treatment. Malnutrition is further aggravated by infections, inflammation, stress, etc. resulting in poor patient outcomes. Therefore, it is imperative that all patients should be assessed for malnutrition with available screening tools. Patient generated subjective global assessment is a simple and inexpensive way for nutritional screening among vulnerable patients and can be utilized at the bedside [38]. Other screening tools like Nutritional Risk Screening 2002 (NRS 2002), the malnutrition universal screening tool (MUST) mini nutritional assessment (MNA) and the malnutrition screening tool (MST) may be utilized as a rapid screening tool, although its use has not been validated in cancer patients. Guidelines recommend the use of performance scales such as the ECOG, or Karnofsky in conjunction with biomarkers such as serum C-reactive protein (CRP) and albumin DEXA (dual X-ray absorptiometry) or bioimpedance analysis (BIA) to assess the nutritional reserve muscle mass and fat for nutritional assessment in high-risk patients [39].

Table 5 Indications of total parenteral nutrition in ICU

Absolute contraindication to enteral feeding	Intestinal obstruction or perforation, necrotizing enterocolitis Worsening hemodynamic instability Mesenteric ischemia
Malfunctioning gut	High output enterocutaneous fistulas Paralytic ileus Massive bowel resection
Inadequate enteral feeding	Patients at a high nutritional risk with anticipated delay in attaining nutritional goals by 7 days Not attaining nutritional goals even after 2 weeks

Regarding feeding, enteral feeding should be initiated early during the ICU stay as it is cheap, safe and continued preferentially as long as it is tolerated. Parenteral nutrition is to be considered in those who are at a high risk of malnutrition and carry contraindications for enteral feeding. Parenteral nutrition is indicated only in a select population in the ICU as described in Table 5 [40]. Even in patients with anorexia, parenteral nutrition has not shown any benefit and priority should always be given to the enteral route if its functioning. Diet fortification with the so called immunonutrition in cancer patients though it seems attractive and physiological is not supported by evidence. Just as any patient with malnutrition these patients are at high risk for refeeding syndrome and needs to be closely monitored for, once the nutrition is initiated [41].

9.1 Recommendations for the Use of Parenteral Nutrition as Put Forward by the American Society for Parenteral and Enteral Nutrition (ASPEN) [42]

1. In cases where there is a contraindication to enteral route or the patient has persistent intolerance to feeds or in cases where they lack adequate bowel function to maintain or restore nutrition status.
2. After 7 days, in adequately nourished patients who are not able to meet at least 50% of the calculated requirements by enteral route.
3. Within 3–5 days in patients at high risk for malnutrition and are expected not to meet the nutritional goals by enteral route.
4. Immediately for patients with moderate or severe malnutrition and enteral nutrition is inadequate.
5. Preoperatively in severely malnourished patients who have intolerance to enteral nutrition.
6. Postoperative for severely malnourished patients who are expected not to tolerate enteral nutrition in 7 days.
7. In patients with advanced disease but having an expected survival of 2–3 months and oral intake or enteral nutrition is not feasible.

10 Outcomes of Critically Ill Cancer Patients

Patients with solid tumors seldom require ICU admission for medical reasons and the most common cause for ICU admission in these groups is for elective postoperative care. However, if they require admission due to medical complications, they have exceedingly high mortality rates compared to normal people [43].

Oncologic emergencies are common in those with hematological malignancy. The common indication for such admissions includes life-threatening medical conditions such as oncologic emergencies, infections or organ dysfunction. They generally tend to have a higher disease severity scores (simplified acute physiology score [SAPS II] or sequential organ failure assessment [SOFA] score) and a higher mortality rate as compared to the general population [44].

Patients who have underwent a Bone marrow transplant (BMT) have high ICU and in hospital mortality, despite a steady decline in mortality rates. Common indications for ICU admission include acute respiratory failure, sepsis, cardiac dysfunction, neurologic disorders, bleeding diathesis, etc. BMT patients requiring mechanical ventilation still have an ICU mortality rate of 80% that further worsens with worsening organ dysfunction. Factors affecting the prognosis of critically ill patients admitted to an ICU are listed in Table 6.

Table 6 Prognostic factors for critically ill oncology patients

Negative	Positive	Neutral
Extremes of age Respiratory failure requiring mechanical ventilation Delay of >2 h in starting appropriate empirical antibiotics Multiple Organ Dysfunction Score >2 organ involvement Higher Apache/ SOFA scores Invasive aspergillosis Poor response of cancer to chemotherapy Poor performance score prior to ICU admission—Karnofsky score <70 or higher Eastern Cooperative Oncology Group (ECOG) scale 3–4	Indication for ICU admission being primary postoperative care Disease in remission Good performance status prior to hospital admission Acute onset of critical illness (<7 days) Absence of fungal infection Absence of comorbidities Reversible cause for ICU admission	Type of tumor (solid vs. hematological) neutropenia, metastatic nature of disease, and prior ICU admission

11 Palliative Care in ICU

In palliative care the primary attempt will be attending to symptom management, empathetic and realistic communication about disease, possible treatment and outcomes and support for both patient and family throughout the course of illness. This is a holistic approach to improve the quality of life of patients and their families, by early identification, meticulous assessment and addressing unmet needs such as pain and other physical, psychosocial and spiritual problems [45]. Palliative care is associated with better control of symptoms, better utilization of resources including ICU stay, increased satisfaction for patient and family and reduced moral stress on the physician, thus minimizing burnout. Examples for palliative care include (but not limited to) addressing pain, thirst, anxiety, dyspnea, etc. The barriers for palliative care should be minimized by effective and realistic communication, discussing advance directives (if present). Palliative care should not be confused with end-of-life care and should be offered to all patients in ICU, especially to those with less than 6 months of anticipated survival at ICU admission, either as an integral part of ICU care or as a part of multidisciplinary care [46].

12 End-of-Life Care (EOLC) in ICU

Ideally only those patients who have a reasonable chance of cure or palliation from their disease or symptoms should be admitted to a critical care unit. However, many a times, patients with advanced disease or those with advanced directives will also be admitted to the ICU for a time-limited full code trial. Although seemingly straightforward, the identification of treatment futility is often vague, delayed and an area of conflict. Unnecessary prolongation of treatment created conflict of interests, increases patient suffering and leads to wastage of resources including manpower. Hence, all attempts should be made to identify futility of care in patients at high risk, being admitted for an ICU trial. If futility is observed, it should be conveyed to the primary team and relatives. An open empathetic communication with relatives and is required both to voice and listen opinions, while avoiding conflict. Care should be taken to avoid confusing terms such as withdrawal of support, mercy killing, etc. [47]. EOLC discussions require time and patience and repeated discussions. Each session must be documented properly to maintain transparency.

Once EOLC is decided, the site of care should be decided, with preference given to patient comfort. Further care to the patient should include avoidance of further aggressive interventions as they increase the sufferings of the patient and maintaining adequate patient comfort. The treatment orders should be reviewed, retaining only medications for symptom control. Unnecessary monitoring should be avoided and close relatives may be permitted to remain by the bedside. Patients should be regular assessed regarding the adequacy of symptom control. The spiritual care should also be taken care, and bereavement support to the family members should be offered to cope with their personal issues [48].

13 Summary

Intensive care in oncology has evolved over decades and is currently a rewarding profession. Properly selected cancer patients admitted to the ICU have survival rates and quality of life identical to their noncancer counterparts. Early identification of sepsis and organ dysfunction along with the use of potent antimicrobial therapies and noninvasive diagnostic strategies for organ dysfunction are some of the factors responsible for the reduction in mortality rates. We need to develop score that identifies those who may benefit from early ICU admission. The strategies used to avoid intubation (like NIV and HFNC) need further evaluation before accepting as an alternative for mechanical ventilation. End-of-life care and palliative care are also integral parts of intensive care and should be offered to all eligible patients. For better outcome of these patients, a multidisciplinary team including intensivist, oncologist and palliative care specialist is essential.

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Vascular Access

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Abbreviations

CR-BSI	Catheter-related bloodstream infection
CVAD	Central venous access device
DTTP	Differential time to positivity
IJV	Internal jugular vein
IVC	Inferior vena cava
PICC	Peripherally inserted central catheter
PVAD	Peripheral VAD
SVC	Superior vena cava
TIVAD	Totally implantable venous access device
VAD	Venous access device

1 Introduction

Venous access represents a vital component in the management of malignancy where patients require surgery, systemic cytotoxic chemotherapy, nutritional support, antibiotics, and intravenous hydration. They are equally necessary in advanced cancers for chronic treatment and palliative measures. Peripheral veins are frequently used for venous access. However, they are not sufficient in several patients with cancer where infusate is of high volume, concentrated or incompatible; therefore, central venous access is necessary. In this chapter, we discuss the types of devices, the insertion techniques, catheter care, and complications related to venous access.

2 Classification of Venous Access Devices

Venous access devices (VAD) are broadly classified into peripheral and central devices. Peripheral VAD (PVAD) are 35–52 mm long Teflon cannulas with various diameters inserted into superficial veins of the arms or sometimes lower limbs in children. They are the most commonly used VAD in clinical practice. They are easy to insert and maintain and are suitable only for short-term use. With countless cannulation and subsequent thrombosis or infection, the loss of peripheral veins presents a problem, especially in cancer patients. The need for a constant search for patent peripheral veins is a reason for pain and anxiety for the patients; consequently, not preferred in many situations in oncology.

The central VADs (CVAD) after insertion have the tip of the catheter at the cavo-atrial junction, the lower third of superior vena cava (SVC), atrium, or upper portion of inferior vena cava (IVC). CVADs are classified into four principal types.

1. Nontunneled catheters are used for short-term continuous venous access (up to three weeks) when peripheral lines are not present or not sufficient for the purpose as in major surgical procedure or the intensive care unit. They are 20–30 cm long polyurethane catheters with a single lumen or multiple lumens. They are safe only for hospitalized patients.
2. Tunneled catheters are used when continuous and long-term venous access (>3 months) is needed. Tunneled catheters are made of silicone. They commonly exit externally on the chest and are inserted into the internal jugular vein (IJV) or subclavian vein. Some of these catheters carry Dacron anchoring cuff providing more stability and prevents accidental removal by pulling [1]. The cuff induces an inflammatory reaction within the tunnel leading to fibrosis and catheter fixation. Tunneling reduces the infection rate and prolongs the life of the catheter [2, 3]. Hickman, Broviac, and Mahurkar catheters are examples of tunneled catheters.

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3. Totally implantable venous access devices (TIVADs) or “chemoports” or simply “ports” are catheters with a chamber attached at one end. The chamber is implanted in a subcutaneous pocket, and the attached catheter is passed through a tunnel and inserted into a central vein, usually IJV or subclavian vein. The chamber is accessed via a specific needle passed through intact skin. They have a lower incidence of catheter-related bloodstream infection compared to other tunneled and nontunneled catheters. Most ports have a single lumen, and they are suitable for long-term intermittent chemotherapy especially in patients with solid tumors. Ports allow no visible tubes outside; they are ideal especially in children as they allow better mobility without the apprehension of accidental removal of catheter.
4. Peripherally inserted central catheters (PICC) are nontunneled central catheters inserted through a peripheral vein of the arm. They are made of silicone or polyurethane and are 50–60 cm long. The tip of the PICC is advanced to reach SVC or right atrium. They are suitable for intermittent use for up to one year. They have a narrow lumen and are more likely to get thrombosis and occlusion due to narrow lumen and reduced flow rate [4]. Catheter migration due to arm movement is likely to produce endothelial damage, cardiac perforation, and rarely arrhythmias [5–7].

3 Valved Catheters

Valved catheters or Groshong catheters carry a slit-like opening on one side of the catheter tip which functions as a valve. The tunneled, nontunneled, or TIVAD can be provided with a valved tip. Force is required to open the valve, and hence positive pressure infusion is required. The valve-like action prevents entry of blood into the catheter tip while allowing the infusate to flow out of the catheter; hence, reduce the chance of infection and thrombosis. However, this has not been proven in a controlled trial. It also eliminates the need for heparin locks and frequent flushing [8].

4 Choosing the Ideal Catheter

There are barely any evidence-based guidelines available on choosing the right access site and the right catheter. Recently, the choosing wisely campaigns recommend the use of peripheral lines whenever feasible and remove invasive catheters as early as possible [9, 10]. The situations in which central venous access is recommended are [11, 12].

1. Peripheral venous access is not available.
2. Prolonged venous access is called for.
3. Multiple lumen infusions are needed.
4. The infusions are not compatible with peripheral lines, like parenteral nutrition containing glucose concentration of more than 10%, amino acid concentration of more than 5%, pH <5 or >9, osmolarity >500 mOsm/L vasopressors, and certain chemotherapy agents with vesicant character.
5. Hemodialysis or plasmapheresis is required.
6. Hemodynamic monitoring of central venous pressure and pulmonary arterial pressure is indicated.

5 Choice of CVAD

There are no randomized trials available for choosing an appropriate device for an individual patient. It is a combined decision by the physician, nurse, and patient considering factors such as duration of treatment, frequency of venous access, the volume of infusate, patient age, patient’s preference, and the ability of the patient’s caregivers to take care of the device.

Nontunneled catheters are used in hospitalized patients for short-term use when peripheral lines cannot be used or they are not available. They are generally used during major surgeries and in intensive-care units. Tunneled VADs are used in patients who need prolonged continuous administration of chemotherapy, antibiotics, parenteral feeding, and blood products and require frequent blood sampling. Tunneled catheters remain the preferred options in patients with hematological malignancies undergoing induction chemotherapy or bone marrow transplantation.

TIVAD are ideal for children in particular and also in adults where long-term intermittent access with infrequent infusion is required as in solid tumors. Those patients who do not want to have any tubing seen outside are offered chemoports that are completely hidden under the skin. PICCs are more suitable for outpatient-based treatment in ambulatory patients with solid tumors.

6 Preoperative Assessment

Comprehensive preoperative assessment including medical history, clinical examination, laboratory investigations, and radiological evaluations is mandatory. Skeletal deformity, scar, obesity, or previous surgery at the insertion site should be recognized beforehand. Preprocedure ultrasound helps in identifying deep vein thrombosis and anatomic variations [13].

Coagulopathy, thrombocytopenia, and neutropenia should be recognized before the procedure and optimized.

7 Technique of Insertion

The insertion of a PVAD is straight forward and generally performed as a bedside procedure. However, the insertion of CVAD is more demanding and can be associated with potential complications especially in inexperienced hands. The technique of insertion of CVAD is discussed here.

Informed consent should be obtained from the patient. The nature of the procedure, need, and potential complications like pneumothorax and bleeding should be explained. The potential need for secondary procedures like chest tube insertion in case of injury should be discussed. Trendelenburg (head low) position is utilized to facilitate adequate venous dilatation and avoid an air embolism. However, hemodynamically unstable patients may not tolerate this position. Routine preoperative antibiotics have not shown benefit; however, institutional protocols for antibiotic prophylaxis should be followed [14]. The patient should be monitored for cardiac rhythm and oxygen saturation throughout the surgery.

CVAD are usually inserted into the IJV or subclavian vein employing a percutaneous approach. The femoral vein is not a favored site due to the high risk of infection in this site [15]. With the introduction of the Seldinger technique for vascular access in 1952, interventional medicine was revolutionized [16]. With the availability of peel away dilator introducer in the 1970s, open surgical vein cannulation is no longer required for venous catheterization. These developments have reduced the complexity of central venous access and helped to perform central venous catheterization as an outpatient or bedside procedure. However, open technique with a venous cut down is still practiced in cases with intraoperative difficulty and in select situations in children.

Nontunneled catheters can be placed at the bed side; however, tunneled catheters and chemoports are inserted in the operating room. The procedure should be performed with strict sterile precautions under local anesthesia with or without sedation or general anesthesia particularly in children and uncooperative patients.

Skin is infiltrated with 1% lignocaine around the site of needle insertion, site of catheter exit, and the tunnel connecting them. Ultrasound guidance helps for the identification of the vein and cannulation under vision. An ultrasound probe is used to locate the vein, and the needle is guided through the skin and into the vessel. Ultrasound guidance reduces the number of unsuccessful attempts and complications and reduces the duration of the procedure [17–21].

When using the landmark method, IJV is accessed between the medial and lateral head of the sternomastoid muscle and subclavian vein is accessed 1 cm below the junction of medial and middle third of the clavicle (Fig. 1). The introducer needle is inserted with negative pressure until venous blood is aspirated. Sometimes there is a risk of piercing the posterior wall of the vein producing a hematoma or even arterial puncture. This complication can be avoided by advancing the needle under image guidance. Once venous blood is aspirated, advancing the needle is stopped, the ultrasound probe is handed over to the assistant surgeon or the staff nurse and the needle is stabilized using the left hand of the operator. The syringe is carefully removed and the guidewire is threaded through the needle hub into the vein. The intravenous position of the guidewire is confirmed with ultrasound, and the introducer needle is removed. Arrhythmia produced by the advancement of the guidewire till the heart is traditionally used as an indication of the correct positioning of the needle; however, we do not consider it as necessary or advisable when the guidewire position can be confirmed using ultrasound.

Sometimes the guidewire may fail to pass into the vein during the introduction. Several reasons have been thought for this as, displacement of the needle out of the vein, hitting the posterior wall of the vein, kinking of the wire within the vein, and coiling against venous junctions. If resistance is experienced, the advancement of the guidewire is instantly stopped, and the needle position is reconfirmed by ultrasound. A minor change in needle direction to make a more parallel angle with the vein sometimes helps to avoid the guidewire striking the posterior wall of the vein. If the resistance persists, the guidewire is withdrawn, the needle position is confirmed by aspiration and the guidewire is reintroduced. Exceptionally, if guide wire fails to pass despite all efforts, one will have to resort to an open method to identify the vein for catheterization. We routinely implement fluoroscopy to confirm the position of the guidewire at this stage though objective evidence is lacking in this practice.

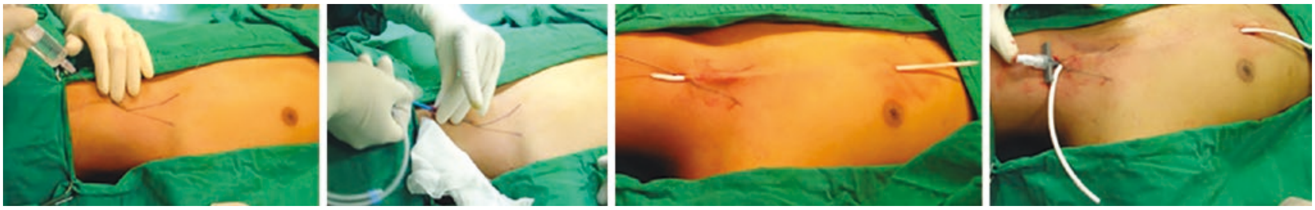

Fig. 1 Sequential clinical images showing the insertion of tunneled central venous access device. The needle is inserted at the apex of the triangle formed by the two heads of sternomastoid muscle. The needle tip is at 45° and directed toward the ipsilateral nipple

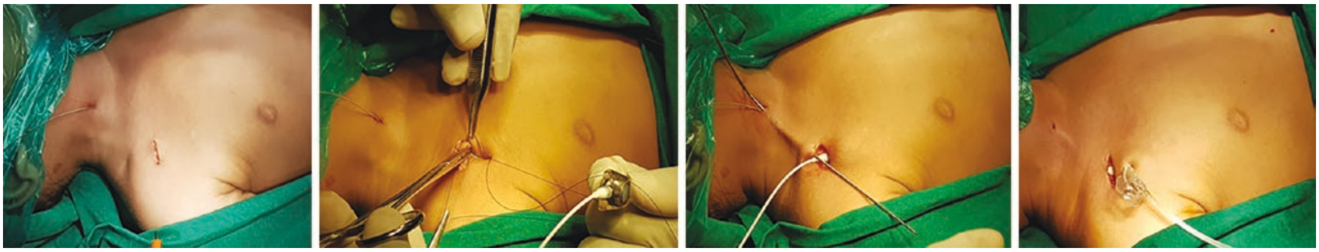

Fig. 2 Sequential clinical images showing the insertion of totally implantable venous access device. The subcutaneous pocket is made in the infraclavicular region, and the chamber is secured with sutures incorporating the pectoral muscles

Once the guidewire is introduced, a small stab incision is made against the wire to increase the opening for the introduction of the dilator. In the case of TIVAD, the attention is directed towards the creation of subcutaneous space for implantation of the chamber. Most commonly the chamber of TIVAD is placed in a subcutaneous plane at the ipsilateral infraclavicular area while the exit site of the tunneled catheter is planned at the inframammary crease between the nipple and sternal border (Fig. 2). However, other areas like supraclavicular fossa, upper back, inner arm, and contralateral infraclavicular area can be chosen depending on the patient's choice, location of the tumor, the field of adjuvant radiation, and local tissue conditions.

An incision is made two fingerbreadths below the clavicle just adequate to introduce the chamber of TIVAD and a subcutaneous space is created. Anchoring sutures are placed with polypropylene, or polydioxanone sutures and parachuting method is used to secure the port chamber firmly on the pectoral fascia and muscle. For the tunneled catheter, the catheter exit site is identified and a small stab incision is made using a scalpel. The tunneling is done to connect the chamber of the port or the catheter exit site to the site of venous access and the catheter is pulled and placed into the tunnel so that in case of the cuffed catheter, the cuff reaches approximately 2.5 cm from the exit site. The length of the catheter is trimmed before insertion in such a way that the tip reaches one centimeter below the sternal angle.

Once the tunnel is constructed, the peel away dilator/introducer is inserted into the vein until the hub touches the skin. Frequent wiggling of the guidewire during the introduction helps to confirm the position of the guidewire and avoid false tracking. After the complete introduction of the dilator, the trocar is removed. Trendelenburg's position is maintained to avoid air embolism. The catheter is placed into the dilator and using thumb it is pushed into the vein. Constant finger pressure is maintained to avoid whiplashing of the catheter out of the dilator. While the thumb exerts pressure on the catheter, the sheath is peeled away and the catheter is inserted completely into the vein.

The Huber needle is introduced into the chamber and the backflow of blood is confirmed and a heparin lock solution is injected. The parachute sutures are tied to secure the chamber and avoid malposition or flipping. Skin sutures on the chamber insertion site are knotted such that the knots do not fall over the chamber. Particular care is observed when skin suture is placed on the accession site to avoid inadvertently taking the wall of the catheter in the suture.

8 Catheter Tip Position

The ideal site for catheter tip placement is continuing controversy. The catheter tip is traditionally placed in the SVC (Fig. 3). However, the catheter tip is liable to migrate to the cavo-atrial junction or right atrium during placement due to excess length or later due to catheter movement. The literature describes unique sets of complications for intracardiac placement as well as intracaval placement of the catheter. Rare complications described specific to intracardiac placement of the catheter tip are dysrhythmia, cardiac perforation, and cardiac tamponade [22–24]. Complications more commonly associated with placement within the vena cava are central venous perforation, hydropneumothorax, hydromediastinum, and venous thrombosis [25–27].

Placement of catheter tip in the upper part of SVC results in an increased incidence of thrombosis compared to placement in the lower SVC or at the cavo-atrial junction [28]. Dialysis catheters placed in the right atrium function better than those placed in the SVC [29, 30]. Unpublished data in pediatric patients using TIVADs for chemotherapy in our center show a higher incidence of catheter thrombosis of 1.99 per 1000 catheter days when the catheter tip was placed in the SVC compared to 1.26 per 1000 catheter days when catheter tip was placed below the cavoatrial junction. In our study, 71 patients had a catheter tip placed in the SVC, and 128 occupied the right atrium.

Traditionally, a postoperative chest radiograph is used for ascertaining the catheter tip position. The angle of the right main bronchus and trachea corresponds to the upper border of SVC and is usually visible on the radiograph [31] Many centers utilize routine intraoperative fluoroscopy to confirm catheter tip position. Recently, ultrasound assessment from right supraclavicular fossa using a micro convex probe is found to be an effective method to visualize catheter tip in the lower SVC and pulmonary artery in a pilot study [32].

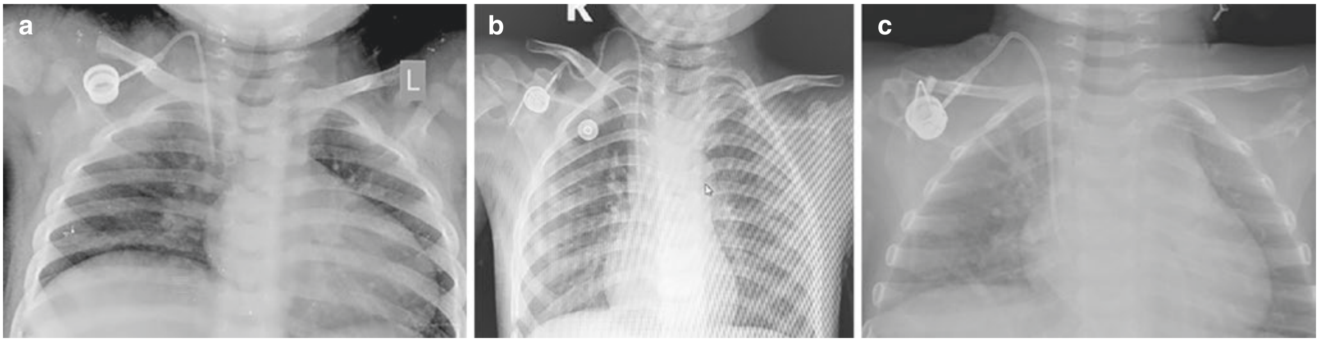

Fig. 3 Chest radiograph showing the catheter tip position in the superior vena cava (**a**), cavoatrial junction (**b**) and below the cavoatrial junction (**c**)

9 Catheter Care

Vascular access devices are flushed and aspirated for blood using a syringe not less than 10 ml capacity (to prevent developing excess pressure within the catheter lumen causing catheter damage) to assess catheter function before each infusion. After use, the catheter is flushed to remove the infusate from the catheter lumen to prevent clogging, and the catheter damage from incompatible medications. Dextrose or components of parenteral nutrition should be meticulously flushed away as they provide nutrients for biofilm formation [33] Flushing using commercially available prefilled syringes helps reduce the incidence of catheter-related bloodstream infection (CR-BSI) [34, 35] compared to intravenous saline preparations [36, 37].

The catheter site should be cleaned and dressings changed every five days when the ports are being used. The access needle should not be left in situ for more than one week. When the port is not used for a long period, flushing of the port with 10 mL of 0.9% saline and locking with heparin saline or 0.9% sodium chloride solution once a month is recommended to prevent catheter block. Randomized controlled trial comparing heparin with 0.9% sodium chloride shows that occlusion rates and toxicity do not differ between the groups [38]. Use of antibiotic lock for prevention of catheter infection is now advocated routinely.

In the case of catheter blocks which are a common problem, the patients need to be treated in the catheter clinic by physicians or trained nurses with a saline injection and aspiration technique. If this does not succeed, urokinase or alteplase injection may help to relieve the block. The vast majority of the catheters can be salvaged with these techniques.

10 Complications Associated with VAD

10.1 Complications of PVAD

The frequent complications associated with PVAD are thrombophlebitis, extravasation injury, hematoma, and bruising [39] Other rarer complications reported are skin necrosis, compartment syndrome, bacteremia, venous embolism, and aneurysm formation [40–42]. Most complications related to PVADs can be reduced by preventing cannulation of veins in the lower extremity, minimizing catheter movement by properly securing, placing the smallest suitable catheter size for the purpose, and removing the catheter as soon as possible [43, 44].

10.2 Complications of CVAD

Serious complications are rare in clinical practice and most are case reports and were reported more than two decades back. The complication of CVAD can be classified into two categories, and they are early complications (occurring intraoperatively or in the initial postoperative period) and late complications.

10.3 Early Insertion-Related Complications

Pneumothorax is a common and serious immediate complication related to central venous access [45, 46]. The most important variable associated with pneumothorax is the operator experience; catheter inserted by a physician with experience of more than 50 prior insertions is half as likely to result in a mechanical complication compared to those by a physician with experience of less than 50 [47]. Subclavian access is more likely to result in pneumothorax compared to IJV cannulation and ultrasound-guided approach to venous access and fluoroscopy guidance to confirm the position of the guidewire within the SVC significantly reduce the incidence [48, 49]. Patients should be observed after the procedure and a routine chest radiograph should be obtained at two hours to rule out pneumothorax or hemothorax. Therapeutic options for iatrogenic pneumothorax include emergency pigtail insertion or a chest tube placement along with administration of oxygen. Asymptomatic, small pneumothorax, in stable patients without preexisting lung disease can be observed and managed conservatively.

Arterial puncture is the most common mechanical complication related to CVAD [50, 51]. The carotid artery, subclavian artery, or femoral artery can be punctured inadvertently. Early recognition of the injury and withdrawal of the access needle and nonocclusive compression of the artery prevents severe bleeding and hematoma. If the artery is dilated or inadvertently catheterized, a vascular repair is indicated and consultation with a vascular surgeon should be sought. In severe cases, injury can lead to arterial thrombosis, stroke, or even death if not acted promptly.

Air embolism occurs when the catheter or the access needle is left open to the atmosphere. It is a dangerous complication and can be lethal. Trendelenburg position and adequate hydration reduce the incidence of serious air embolism. The patient suffers from acute onset dyspnea, cough, chest pain, and collapse if significant air enters the circulation. Left lateral decubitus and Trendelenburg position help to trap air in the right ventricle. 100% oxygen helps in early absorption of air [52].

Ventricular arrhythmias and bundle branch block are recognized complications. During the procedure, the entry of metallic guidewire in the right atrium causes arrhythmias, but it is usually limited [53]. Persistent symptomatic arrhythmia is rare, but if present, the catheter has to be repositioned or removed. Catheter malposition into the subclavian vein or brachiocephalic vein requires reinsertion or re-fixing for adequate function.

10.4 Late Complications

Late complications can be segregated into infectious complications and mechanical complications. They are bloodstream infection, pocket infection, thrombosis, catheter dysfunction, catheter rupture, migration or embolization, pinch-off syndrome, SVC erosion and perforation, cardiac perforation and tamponade, extravasations, and port inversion [54–58]

10.4.1 Infection

Catheter-related infections are classified into three: exit site infection, tunnel infection, or systemic infection (CR-BSI). Most exit site infections and tunnel infections are caused by *Staphylococcus aur*eus. It is manifested by local inflammation, erythema with or without purulent discharge. Most cases are not associated with bacteremia. They can be treated with antibiotics and catheter removal is necessary only in cases that do not respond to antibacterial therapy [59, 60] Implementing sterile technique during insertion, skin antisepsis during catheter use and maintenance, use of antibacterial catheter, and antibacterial catheter lock solution help to reduce the infectious complications.

Systemic infection (CR-BSI) is a more serious condition. They arise either from the spread of the infection from the exit site or the contaminated catheter hub. It is often a challenge to diagnose CR-BSI in clinical practice. They are more common among nontunneled central catheters compared to tunneled ones, PICC and TIVAD and ranges from 1.1 to 2.7 per 1000 catheter days [2] Unpublished data from our center shows that among 203 pediatric patients who received TIVAD, the rate of infection was 0.15/1000 catheter days. Differential time to positivity (DTTP) is a reliable diagnostic tool for identifying CR-BSI. Blood is collected from the CVAD as well as peripheral blood. If the blood from CVAD shows positive growth at least 2 h before the peripheral blood, diagnosis of CR-BSI is confirmed. Empirical antibiotics are initiated after culture samples are obtained. On diagnosis of CR-BSI, nontunneled catheters should be removed, whereas an attempt may be done to preserve tunneled catheters or TIVAD with appropriate antibiotics based on blood cultures and antibiotic lock therapy, provided patient's health condition remains stable.

10.4.2 Mechanical Complications

Catheter thrombosis is the most common complication, and it is due to clots, lipid aggregates, drugs, or contrast agents. Appropriate flushing and locking the catheter as discussed above keep the incidence of catheter block low. In case of irreversible catheter block exchange over the guidewire or removal becomes necessary.

Tip migration occurs due to increased intrathoracic pressure when the catheter is placed inappropriately high in the SVC. It can be prevented by proper positioning. Pinch off syndrome is the compression of the catheter between the first rib and clavicle especially in the case of the catheter in the subclavian vein and usually happens after blind placement through the infraclavicular route. This results in catheter occlusion, malfunction, damage, or fracture. Catheter rupture is a rare complication, and the ruptured segment needs to be retrieved from the pulmonary vessel using interventional radiological procedures.

Damage to the external part of VAD or erosion of the tissue over the catheter chamber happens due to inadequate nursing care and is usually preventable. Catheter dislocation of the tunneled catheter can be prevented by positioning the cuff at least 2.5 cm for the insertion site and that of a nontunneled catheter by proper stabilization. Flipping of the catheter chamber of TIVAD results in malfunction and can be avoided by proper fixation. Cardiac perforation and tamponade are very rare complications of central venous use [61].

11 Special Concerns of CVAD in Pediatrics

Prolonged central venous access is particularly important to children where repeated search for peripheral veins and cannulation is a cause for pain and anxiety for the children as well as the parents and even health care workers. As discussed above, the friendliest option for kids is TIVAD as there is no tubing outside, do not hinder bathing and playing and they require minimal maintenance to keep the device patent. However, in the case of hematologic cancers notably when bone marrow transplantation is planned, a Broviac catheter is preferred.

The insertion of CVAD is more challenging in children due to the small caliber vein, especially in neonates. In select cases with difficulty, an open method with a venous cutdown is considered [62]. Infectious complications are found to be higher in children especially below 2 years [63–65] though the incidence is generally low.

12 Summary

- Central venous access is preferred over peripheral access when prolonged venous access and high volume, concentrated, or incompatible infusion is required.
- CVAD include tunneled catheters, nontunneled catheters, TIVAD and PICC and the choice depends on type and volume of infusate, duration and frequency of treatment, age and choice of the patient.
- Nontunneled central catheters can be inserted at the bedside, whereas tunneled catheters and TIVAD are inserted in the operating room under controlled conditions.
- Insertion-related complications are infrequent with CVAD and is further reduced by the physician experience and use of ultrasound-guided insertion technique.
- Long-term complications of CVAD include infectious and mechanical complications, and they can be reduced by improvising the technique of insertion, improving the quality of catheter care by utilizing dedicated and trained nurses, and equipping the patient's caregivers with knowledge about catheter care.
- Young children suffer infectious complications from CVAD, though the incidence generally remains low.

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Comorbidities in the Cancer Patient

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Abbreviations

ADT	androgen-deprivation therapy
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence interval
CVD	Cardiovascular diseases
CVD-IP	Collagen vascular disease-associated interstitial pneumonia
DM	Diabetes mellitus
HM	Hematological malignancies
HT	Hypertension
IGF	Insulin-like growth factor
IGRA	Interferon-gamma release assay
IPF	Idiopathic pulmonary fibrosis
IRR	Incidence rate ratio
LTBI	Latent tuberculosis infection
PCI	Percutaneous coronary intervention
RP	Radiation pneumonitis
TB	Tuberculosis
TST	Tuberculin skin test
UIP	Usual interstitial pneumonia
VEGF	Vascular endothelial growth factor

1 Introduction

Comorbidity is a long-term health condition affecting a patient in addition to the index disease. With changing demographics there are increasing number of people over the age of 60 years [1]. With improved life expectancy incidence of both cancer and comorbidities of noncommunicable types are likely to increase. Comorbidities can impact the cancer stage at diagnosis. This impact varies considerably by cancer type, individual comorbid condition and overall comorbidity burden [2]. Presence of co morbidities may affect the decisions related to treatment of cancer or tolerance to cancer treatment, and thus, they may impact cancer outcomes [3]. Comorbidities may pose competing risks for morbidity and mortality in patients with cancer and could be a major confounder in clinical trials [1]. It is observed that cancer patients with higher rates of comorbidity have 1.1 to 5.8-fold higher mortality risk [4]. The risk of major toxicity and hospitalization due to chemotherapy is increased in cancer patients with comorbidities [5–7].

Comorbidity is a multidimensional variable and several scoring indices have been developed to measure comorbidity. Some of the indices are Charlson comorbidity index, Cumulative Illness Rating Scale, Kaplan–Feinsten Index, National Institute on Aging/National Cancer Institute comorbidity index, Adult Comorbidity Evaluation-27 and the Elixhauser method [8–13]. The prevalence of measured comorbidity will vary depending on the measure of comorbidity used, the study population and the cancer type [14]. There is lack of consensus about the best approach to measuring comorbidity burden in cancer patients and the choice of measure may vary depending on the study question, population studied and data available [14].

In patients aged 65 years or older, four of ten patients with cancer had at least one other chronic condition recorded and 15% had two or more as per data from Medicare beneficiaries in the United States. Cardiovascular disease, obesity and metabolic disease, mental health problems, chronic obstructive pulmonary disease and musculoskeletal conditions were the most common chronic conditions recorded in these patients [15]. India faces the dual burden of chronic noncommunicable diseases and communicable diseases [16]. In India, cardiovascular diseases (coronary heart disease, stroke and hypertension) contribute to 45% of all noncommunicable diseases and deaths, followed by chronic respiratory dis-

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ease (22%), cancer (12%) and diabetes (3%) [17]. Among communicable diseases in India, tuberculosis contributes the largest number of new cases annually compared to any other country in the world [16]. In a study of breast cancer patients from India 75% of the comorbid conditions were chronic diseases such as hypertension (21.8%), chronic obstructive pulmonary disease (19.9%), rheumatoid arthritis (18.6%) and diabetes mellitus (16.7%) [18].

2 Cardiovascular Diseases

Cardiovascular diseases (CVD) are a leading cause of mortality globally, accounting for 31% of all deaths, followed by cancers, respiratory diseases and diabetes [19]. CVDs are also the leading cause of mortality in India [20]. As per the Global Burden of Disease study, estimate of age-standardized CVD death rate of 272 per 100,000 population in India is higher than the global average of 235 per 100,000 population [21]. With aging population and increased longevity due to advances in cancer therapeutics, the overlap of CVD and cancer is likely to increase [22, 23].

Modifiable risk factors like obesity, diabetes mellitus (DM), hypertension (HT), physical inactivity, diet and tobacco use are common risk factors for both cancer and CVD [24–28]. Obesity, diabetes mellitus, hypertension, CVD and cancer have a complex relationship mediated by several factors such as hormones (sex hormones, insulin and insulin-like growth factor [IGF]), proinflammatory cytokines and adipokines (interleukin 6, tumor necrosis factor alpha, leptin, resistin), angiogenic factors and oxidative stress [29–34]. Obesity has been linked to esophageal, pancreatic, liver, colorectal, postmenopausal breast, endometrial and kidney cancer [35]. Type 2 DM and HT are also linked with certain cancers [25, 36]. Several studies have examined the impact of antidiabetic and cardiovascular medications on cancer incidence (insulins, antihypertensive drugs, aspirin) and on cancer outcomes (metformin and statins) [37–42]. Metformin has been shown to decrease cancer incidence and increase in cancer specific survival in some studies [41].

Coronary artery disease (CAD) is the most common cardiovascular disease. The aim of treatment in patients with CAD is to control symptoms and prevent progression into acute coronary syndrome or infarction [43]. In addition to medical treatment (beta blockers, statins, antiplatelet and angiotensin converting enzyme inhibitors), some patients may require coronary revascularization. The options include percutaneous coronary intervention (PCI) without stent, PCI with bare metal stent or with drug-eluting stent and coronary artery bypass graft (CABG) with or without extracorporeal circulation [44]. In patients in whom coronary revascularization is indicated, the severity of the cardiac disease, the stage of the malignancy and the general condition of the patient should be taken into consideration while choosing the method of revascularization. PCI is preferred if the malignancy is aggressive or widespread. In cancer patients with thrombocytopenia who are planned for PCI, appropriate antiplatelet and heparin dose should be used to avoid bleeding complications [45]. In indicated cases, CABG is a good option only when the malignancy is potentially curable [45]. Cardiac risk factors including hypertension, diabetes, dyslipidemia should be managed optimally [46]. A thorough clinical evaluation should be done to determine the baseline cardiovascular risk as per standard guidelines in all patients receiving cancer directed treatment [47].

Some cancer therapies are also linked with cardiovascular injury, increasing CVD susceptibility via the multiple-hit hypothesis [48]. A wide range of chemotherapy agents have been associated with cardiotoxicity (Table 1). The most frequent cardiotoxicity is asymptomatic or symptomatic left ventricular dysfunction [49]. Other cardio toxic effects include hypertension [50], thromboembolic disease [51], pericardial disease [52], arrhythmias [53] and myocardial ischemia [54]. Radiation therapy where treatment field involves the heart can also lead to coronary artery disease and fibrotic changes of the valves, pericardium and myocardium [55, 56]. These patients may present years or decades after exposure to radiation treatment. With increased longevity due to modern cancer therapeutics, cancer survivors are being exposed to potential comorbidities due to nononcologic side effects of anticancer therapy [57].

In patients receiving treatment for cancer and in cancer survivors, early detection of cancer directed treatment-induced cardiovascular injury, accurate diagnosis and management of cardio-toxic events may improve long-term cardiac outcomes [58]. Early detection of cardiac injury may facilitate early therapeutic measures [59]. Implementation of appropriate monitoring plans as per potential cardiovascular risk are recommended by many guidelines [47]. Cardio oncology is evolving as an important subspecialty which aims is to assist in the overall cardiac care of cancer patients from the initial assessment to survivorship through an integrated approach [60].

Table 1 Systemic anticancer drug-induced cardiotoxic effects [49–53]

Type of cardiovascular toxicity	Drugs
Left ventricular dysfunction	*Anthracyclines/analogues*—Doxorubicin, Epirubicin, Mitoxantrone *Alkylating agents*—Cyclophosphamide, Ifosfamide *Antimicrotubule agents*—Docetaxel *HER 2 receptor Mab*[a]—Trastuzumab *VEGF A Mab* [a]—Bevacizumab *Small molecule TKI* [a]—Sunitinib *Proteasome inhibitors*[a]—Bortezomib, carfilzomib *Immune checkpoint inhibitors*—Nivolumab, Pembrolizumab, Ipilimumab
Myocardial ischemia	*Pyrimidine analogues*—Capecitabine, 5 Fluorouracil *Antimicrotubule agents*—Paclitaxel, Docetaxel, *Alkylating agent*—Cisplatin *VEGF A Mab*[a]—Bevacizumab, *Small molecule TKI*[a]—Erlotinib
Hypertension	*VEGF inhibitors*[a]—Bevacizumab, *Small molecule TKIs*[a]—Sunitinib, Sorafenib, Pazopanib. *Alkylating agent*—Cisplatin *Proteasome inhibitor*—carfilzomib
Pulmonary hypertension	*Small molecule TKI*[a]—Dasatinib
Venous thromboembolism	*Alkylating agent*—Cisplatin *Angiogenesis inhibitors*—Thalidomide, Lenalidomide *VEGF A Mab*[a]—Bevacizumab
Arrhythmias	
Bradycardia	*Antimicrotubule agent*—Paclitaxel *Angiogenesis inhibitor*—Thalidomide
QT prolongation	*Arsenic Trioxide* *Small molecule TKIs*[a]—Lapatinib, sunitinib, Crizotinib, dasatinib, nilotinib, Ribociclib
Supraventricular tachyarrhythmias	*Small molecule TKIs*[a]—Ibrutinib, Ponatinib, Sorafenib *Proteasome inhibitor*[a]—Carfilzomib *Anthracyclines* *Alkylating agent*—Cyclophosphamide *Pyrimidine analogue*—Capecitabine

TKI tyrosine kinase inhibitor, *Mab* monoclonal antibody

[a] Targeted therapy

3 Hypertension

Hypertension is a common chronic disease and modifiable risk factor for CVD, cerebrovascular diseases and chronic kidney disease. As per 2010 data, 31.1% of the world's adults are hypertensive, 28.5% in high-income countries and 31.5% in low- and middle-income countries [61]. About 33% urban and 25% rural Indians are hypertensive [62]. In India, hypertension is the leading noncommunicable disease and attributing for nearly 10% of all deaths [21]. HT has been reported to be the most common comorbidity in patients with cancer accounting for 37% of all comorbidities [63]. New-onset hypertension, regardless of severity, was observed in about one-third of cancer patients with various types of solid tumors [64]. The prevalence of hypertension and cancer both increases with aging and is thus likely to increase with aging population.

The association between hypertension and higher risk of renal cancer is well described, and in a recent meta-analysis, it was suggested that hypertensive individuals may be at a higher risk of postmenopausal breast cancer, uterine adenocarcinoma and colorectal cancer than nonhypertensive individuals [36]. Chronic renal hypoxia and lipid peroxidation with formation of reactive oxygen species are hypothesized biologic mechanisms underlying the association between hypertension and renal cancer [34, 65].

Higher rates of hypertension are observed after the initiation of certain systemic anticancer treatments traditional (alkylating agents) and newer targeted therapies (Vascular endothelial growth factor signaling pathway (VSP) inhibitors, Bruton's tyrosine kinase inhibitor, proteasome inhibitors and epidermal growth factor receptor tyrosine kinase inhibitors) [66–69] (Table 1).

The probable mechanisms for VSP inhibitor-induced HT are endothelial dysfunction secondary to reduced nitric oxide bioavailability, increased vascular and renal endothelin production, increase in vascular tone, vascular rarefaction and renal thrombotic microangiopathy with secondary glomerular structural and functional changes that lead to proteinuria and hypertension [70–72]. Alkylating agents can cause HT due to endothelial dysfunction and arterial vasoconstriction [73]. Steroid-induced hypertension is likely due increased patient's sensitivity to vasoactive substances and salt and fluid retention [74]. In patients with head and neck cancer, surgery or radiation therapy that involves the head or neck is associated with difficult-to-treat labile hypertension and hypertensive crisis likely due to baroreflex failure [75].

HT is also an important risk factor for chemotherapy-induced cardiotoxicity [76]. In patients who developed HT after receiving VSP pathway inhibitors, HT was associated with better progression free and overall survival [67]. Patients with hypertension should receive guideline directed therapy while taking into consideration the associated comorbidities and potential drug–drug interactions [77]. Optimal management of hypertension will minimize the risk of end-organ damage and allow completion of cancer therapy. The angiogenesis task force of the National Cancer Institute investigational drug steering committee has also issued recommendations for the prevention and management of hypertension in patients receiving angiogenesis inhibitors [78].

4 Diabetes

India has the second highest number of patients with diabetes in the world [79]. Prevalence of DM among newly diagnosed cancer patients is estimated to be 8–18% [80]. The risk of death increases by 40% in patients having DM at the time of cancer diagnosis [81]. High blood sugar levels with or without prior history of diabetes will develop in 32–60% of cancer patients [82–86]. Cancer patients with metabolic disease carry high risk of tumor recurrence, metastasis or fatal outcome than those cancer patients without metabolic disease [87]. Certain systemic anticancer therapies and steroids can cause high blood sugar levels in patient undergoing cancer treatment.

Type 2 DM has been associated with breast, intrahepatic cholangiocarcinoma, colorectal and endometrial cancer, with inconclusive or no evidence for an association with other cancer sites [25]. Risk factors such as aging, obesity, dietary habits, physical inactivity are common to both diabetes and cancer [88]. The interlink between diabetes and cancer is complex with multiple cascades at molecular levels. Hyperinsulinemia, insulin resistance, hyperglycemia, obesity and mediators of chronic inflammation are all markers of carbohydrate metabolism dysfunction which play a major role in mechanisms promoting cancer development and progression in patients with DM [89]. High blood glucose levels have the ability to prevent cancer cells from apoptosis process and thus leading to more aggressive cancer phenotype [90]. The apoptosis-promoting effects of metformin an oral hypoglycemic agent on different cancers by increase of apoptotic genes have been demonstrated [91, 92]. It was observed that pioglitazone increases risk of bladder cancer although this risk was not statistically significant, the increased risk, as previously observed, could not be excluded [93].

L-asparaginase, a cytotoxic chemotherapeutic agent, can induce hyperglycemia through both direct and indirect effects [94]. In patients with baseline impaired glucose tolerance, steroids cause postprandial glucose elevation. However, it is important to note that nondiabetic patients can also develop corticosteroid-induced hyperglycemia [95–97]. This generally reverts back to normal after stopping of steroids; however, it is important to address in order to avoid short-term complications [97], Mammalian target of rapamycin (mTOR) inhibitors may increase total cholesterol, triglyceride and glucose levels [98]. New-onset autoimmune DM has been reported with immune checkpoint inhibitors [99]. Androgen-deprivation therapy (ADT) with luteinizing hormone-releasing hormone [100], chemoradiation [101], platinum-based chemotherapy [102] and 5-fluorouracil-based chemotherapy [103] have also been associated with hyperglycemia.

In a meta-analysis of postoperative mortality across all types of cancer, the risk was increased in patients with pre-existing diabetes (odds ratio 1.51 [1.13–2.02]), compared with nondiabetic patients undergoing operative cancer management [104]. Hyperglycemia during chemotherapy for hematologic and solid tumors is correlated with increased toxicity [105]. Assessment of patients-associated comorbidities and diabetes-related cardiac, renal or neurologic complications should be done, and patients are managed as per existing guidelines. The focus of managing hyperglycemia in patients who are ongoing active cancer treatment should be on avoiding acute and subacute outcomes such as dehydration from polyuria, infection, catabolic weight loss, hyperosmolar nonketotic states and diabetic ketoacidosis [106].

5 Chronic Obstructive Pulmonary Disease (COPD)

The existence of comorbidities in lung cancer can impact not only survival but quality of life as well [107, 108]. WHO reports that 3.0 million lives were lost due to chronic obstructive pulmonary disease in 2016, while 1.7 million died of lung cancer. Data suggests a COPD prevalence of around 50–80% in lung cancer. In a Danish study, COPD was coexistent in 68% of lung cancer patients [109]. Indian data showed a COPD prevalence of 41.9% in lung cancer [110]. The risk of lung cancer in COPD is approximately 167 per 10,000 person-years as compared to the overall risk of 6.1 per 10,000 person-years [111]. The relationship is reciprocal and lung cancer was noted as a leading precursor of death in patients with early COPD [112].

Emphysema was an indicator of poor overall survival independent of tumor staging [113]. Poor lung function and overall poor performance status due to COPD may often be a cause for deferring or delaying a curative lung surgery [114]. In a series of 455 patients with COPD and lung cancer, those with severe COPD had reduced cumulative survival after 2 and 5 years compared to patients with nonsevere COPD. There was a 69% increased risk of mortality in patients who had severe COPD [110]. A meta-analysis of six studies of COPD and postresectional lung cancer concluded that COPD was associated with lower overall survival, prolonged mechanical ventilation and higher rates of pneumonia [115]. Other potential contributory factors that worsen cancer quality of life as well as affect overall survival are systemic cachexia and sarcopenia. These are often found in both COPD and lung cancer due to the effects of pro-inflammatory cytokines such TNF α IL-6. It also leads to poor tolerance to therapy, poorer functional status and decreased quality of life [116].

In the light of the above associations, the detection of COPD in lung cancer patients and its optimal management is an essential component to improve lung cancer survival and surgical outcomes. In a Danish study, among lung cancer patients, only 31% of COPD patients had been diagnosed and only 33% had received guideline appropriate treatment prior to enrolment in the study [109]. COPD management is a multipronged approach, and it includes appropriate pharmacotherapy, pulmonary rehabilitation, nutritional rehabilitation and identification and addressing of issues such as depression related to chronic illness. The role of pulmonary rehabilitation in this context is noteworthy. Pulmonary rehabilitation including exercise training that includes both endurance and resistance training improves muscle mass, muscle strength and exercise capacity. Also, pulmonary prerehabilitation ahead of lung cancer surgery improves lung function recovery and may reduce postoperative complications such as pneumonia, prolonged air leak, respiratory failure and empyema [117]. Pulmonary rehabilitation in COPD is recommended at a minimum of 2 sessions a week for 6 weeks. However, in the context of cancer patients waiting for surgery, it may not be possible to postpone surgery for this long, the main concerns being disease progression and patient and care taker anxiety. Shorter programs up to 4 weeks have also shown promise, but studies saw poor recruitment due to patient reluctance to wait for so long [118]. Pharmacotherapy for COPD is as per the GOLD guidelines and includes use of bronchodilators, including beta 2 agonists and anticholinergics and inhaled steroids in severe COPD patients with frequent exacerbations. Optimization for COPD is essential even for improving preoperative or prechemoradiation lung functions in this section of patients who already have compromised functions at baseline.

Ferguson reported that a respiratory physician consultation in the early course of assessment increased the probability of lung cancer patients being treated with surgery, radiotherapy, or chemotherapy [119]. Patients with a prior pulmonologist consultation had higher survival rates with estimated survival rates of 24.4% versus 11.1% for 1-year and 8.1% versus 3.7% for 3-year survival. Janaki et al. noted that surgical rates were significantly lower in patients who did not receive a pulmonologist involvement than in those who had a pulmonologist consult. This study also indicated that among patients with early COPD, there was a 20% reduction in mortality risk (HR 0.80 95% CI 0.75–0.85) if they were under treatment by a pulmonologist [120]. Pharmacotherapy, pulmonary physiotherapy and rehabilitation can improve lung functions, cachexia and exercise capacity along with a significant role in reduction of postoperative morbidity and most importantly overall survival, thus emphasizing on a multidisciplinary management of all cancer patients with COPD with a multipronged approach.

6 Interstitial Lung Disease (ILD)

Smokers are at risk of developing ILD as well as lung cancer. Patients with Idiopathic pulmonary fibrosis (IPF) have a relative risk of 7–14 of developing lung cancer as compared to the general population [121–124]. Two to 4% of collagen vascular disease-associated interstitial pneumonia (CVD-IP) patients may develop lung cancer [125, 126]. In various studies [127–130] the incidence of ILD ranges from 2.2 to 3.9% in patients with NSCLC. The prevalence of lung cancer at time of initial diagnosis of ILD has been reported as 6, 17 and 15% [131–133].

Preexisting ILD (PE-ILD) is a risk factor for drug-induced ILD as well as for acute exacerbation of ILD on cancer therapy and impacts subsequent therapy, outcome and quality of life. Presence of PE-ILD is indicative of a poor prognosis for surgical outcomes in lung cancer patients with higher risk of ARDS and acute exacerbation of ILD (AE-ILD) [134–139]. Postoperative complications leading to mechanical ventilation and death were more likely to develop in ILD patients than non-ILD patients [127, 129, 130]. In a review of 50 patients with ILD and lung cancer who were operated, 24% developed an acute exacerbation within 30 days of resection with a high mortality [140]. Fujimoto reported a mortality rate of 36% due to interstitial pneumonitis in lung cancer patients on cancer therapy. Development of pneumonitis was independently associated with pre-existing ILD. Pneumonitis was an independent predictor of overall survival (OS). Performance status worsened after the pneumonitis improved in 62% of survivors and 54% of survivors received no further systemic anticancer therapy once they developed pneumonitis [141].

Asai et al. in their study of 46 patients with pre-existing ILD and lung cancer, observed that chemotherapy-induced AE-ILD developed in 32.6%. They also noted that this AE-ILD was more likely to develop in a usual interstitial pneumonia (UIP) pattern or possible UIP pattern of ILD than in a pattern inconsistent with UIP (80% vs. 9.7%). A UIP or possible UIP pattern of ILD was an independent risk factor for chemotherapy-induced AE-ILD on multivariate analysis [142]. Yano reported an incidence of AEILD of 30.6% in their series of 86 patients with pre-existing ILD and lung cancer [143]. Togashi reported that preexisting ILD is an independent prognostic factor for poorer survival in their series of small cell lung cancer [144]. Johkoh reported that drug-induced was more likely to develop in patients with pre-existing ILD and especially if the remaining normal lung is less than 50%. The risk of developing fatal drug-induced ILD was high if the amount of normal lung tissue remaining was less than 50% [142].

The risk for developing radiation pneumonitis (RP) following conventional and stereotactic body radiation therapy (SBRT) is higher in patients with preexisting ILD [145–149].

In Ueki's study, the incidence of ≥Grade 2 RP was 55.0% and that of ≥Grade 3 RP was 10.0% in patients with preexisting ILD. Preexisting ILD was an unfavorable prognostic factor for NSCLC patients treated with either chemotherapy or surgery [128, 138, 139, 150].

ILD also adversely affects survival [129]. The 5-year survival rates in pathologic stage IA lung cancer patients with idiopathic pulmonary fibrosis (IPF) were 54.2% and in those without IPF were 88.3% in Saito's study [151].

7 Tuberculosis

Tuberculosis (TB) and cancer are public health problems contributing to mortality of 1.7 million and 8.8 million deaths, respectively, globally. Seven countries accounted for 64% of the 10.4 million cases of TB in 2016, with India leading the count [152–154] Simonsen et al. showed that the risk of developing TB was highest 3 months preceding and immediately postcancer diagnosis, perhaps due to lowered immunity due to the cancer. This risk remained elevated beyond 5 years of follow-up with HR of 2.48 (95% confidence interval [CI]: 1.99–3.10) [154]. A retrospective analysis from China, of data from a self-reported questionnaire, reported that patients with tuberculosis had an eightfold higher (25 vs. 3.1 per 1000 person-years) risk of lung cancer mortality than those without [155]. Tobacco use while contributing to 22% cancer deaths also increases risk for tubercular disease and death.

In a meta-analysis, adult patients with cancer had an incidence rate ratio (IRR) of TB of 2.61 (95% CI 2.12–3.22).The IRR was 3.53 (95% CI 1.63–7.64) in hematological malignancies (HM), and in solid cancers in adults, it was 2.25 (95% CI 1.96–2.58) with head and neck cancers and then lung cancers leading the count [156]. Similar findings have been noted in our center as well. This is due to altered Th1 response due to HM itself as well as chemotherapy, monoclonal antibodies and immunosuppressive condition of hematopoietic stem cell transplantations. Additionally, cancers of the aerodigestive tract cause weakening of the local barriers predisposing to TB [157]. Fujita et al. identified that old radiologic changes were seen at initial evaluation and before initiation of cancer treatment more commonly in cancer patients who developed TB. They also noted that chest radiograph with fibro-nodular disease, was a risk factor for the development of active TB emphasizing the need for x ray chest prior to initiation of cancer treatment [158]. Relying only on Pet imaging to diagnose metastatic disease without histopathological confirmation in high TB burden countries may inadvertently upstage the malignancy as TB can mimic cancer in PET [159, 160]. While treatment of tuberculosis is as per national guidelines, oncologists need to bear in mind the Cytochrome CYP3A4 induction by Rifampicin (R) reducing the serum levels of drugs like erlotinib, gefitinib, imatinib, dasatinib, etc. which are metabolized hepatically, primarily by CYP3A4. Tuberculosis delays the initiation of cancer treatment. Anticancer therapy is usually started 2 weeks after initiation of antitubercular therapy when infectivity is considered to be decreased. However, since this may result in treatment delay, it could result in cancer progression, which could negatively affect the prognosis.

8 Latent TB Infection (LTBI)

Approximately one-fourth of the world has latent TB (have been infected by TB bacilli but have not developed disease) with a 5–15% lifetime risk of developing disease. Though WHO recommends either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) to test for LTBI, a combined approach with tuberculin skin test and different interferon-γ release assays might be the best option (after ruling out active disease). This is due to the lower sensitivity of IGRA in resource-poor settings contributed by low immunity of patients (either due to advanced disease, HIV or malnutrition), blood collection errors, or poor assays [161, 162]. Most TB guidelines do not address the risk factors for developing active TB in the cancer patient population nor do they address the possibility of latent tuberculosis infection (LTBI) in cancer patients or discuss the need for LTBI treatment in these immunocompromised patients. WHO guidelines recommend testing and treatment for LTBI in patients who are preparing for an organ or hematological transplant, receiving dialysis, being started on anti-TNF treatment and silicosis, because of the high risk of LTBI progressing to active TB disease in these patients. WHO recommends Isoniazid (H) monotherapy for 6 months/3 month daily or weekly H and R for LTBI treatment in both adults and children in countries with high and low TB incidence [163]. Notably, besides the above mentioned factors, hematologic malignancies, immunosuppression and head and neck cancers have been identified by US and Canadian guidelines as important risk factors for developing active tuberculosis and recommend screening for LTBI [164–166]. Presently, there are no established local guidelines and policies for screening and treatment of LTBI in cancer patients in high TB burden countries like India.

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Hereditary Cancers

Rajiv Sarin

Abbreviations

ACMG	American College of Medical Genetics and Genomics
AMP	Association for Molecular Pathology
CMMRD	Constitutive mismatch repair deficiency
ELSI	Ethical, legal and social issues
GoF	Gain of function
HGVS	Human Genome Variation Society
IARC	International Association for Research in Cancer
ICGC	International Cancer Genome Consortium
incRNA	Intervening noncoding RNA
InSiGHT	International Society for Gastrointestinal Hereditary Tumors
LGR	Large genomic rearrangement
LoF	Loss of function
LOH	Loss of heterozygosity
LOVD	Leiden Open Variation Database
MAP	MUTYH-associated polyposis
MTC	Medullary thyroid cancer
PBL	Peripheral blood lymphocytes
PCR	Polymerase chain reaction
RB	Retinoblastoma
TCGA	The Cancer Genome Atlas
TSG	Tumor suppressor genes
XP	Xeroderma pigmentosum

1 Principles of Genetics in Oncology

The genetics of cancer encompasses its hereditary aspects and germline mutations as well as the genetic mechanisms underlying cancer development through somatic mutations. Hanahan and Weinberg in the year 2000 described six hallmarks of cancer-sustaining proliferative signaling, resisting cell death, enabling replicative immortality, evading growth suppressors, inducing angiogenesis and activating invasion and metastasis. They subsequently added two hallmarks—reprogramming of energy metabolism and evading immune destruction along with two enabling characteristics—tumor promoting inflammation and genomic instability and mutation [1]. Genomic instability and mutations play a central role in the complex process of cancer development, cancer metastases and resistance to therapy.

Until the 1960s, cancer genetic studies were confined to syndrome description, patterns of inheritance and cytogenetic abnormalities of hematological and pediatric cancers. A series of ground-breaking discoveries in the 1970s and early 1980s, all awarded with the Nobel Prize, radically changed our understanding of cancer biology and genetics. These included discoveries of oncogenes causing cellular transformation by Harold Varmus and Michael Bishop [2] at the University of California, San Francisco (UCSF); the recombinant DNA technology by Paul Berg and other scientists at the Stanford University and UCSF; Sanger sequencing by Frederick Sanger in Cambridge; and the polymerase chain reaction (PCR) by Kary Mullis in California. The Human Genome Project, launched in 1990 by the US National Institute of Health (NIH) and Department of Energy and joined by the UK Wellcome Trust Sanger Institute and other centers in Germany, France, China and Japan, reported the "draft human genome" in the year 2000 and the "complete human genome" in the year 2003 [3]. Unprecedented developments allowed continued reduction in time and cost of genome sequencing, making it one of the very few large-scale technologies to defy Moore's law of doubling of "compute power" every 2 years [4]. This set the stage for large scale cancer genome projects like The Cancer Genome Atlas (TCGA) of the United States and the International Cancer Genome Consortium (ICGC), in which India is one of the founding members [5]. These studies established the genomic landscape of diverse cancers and identified key genes and mutations that could be used in precision medicine and can-

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cer risk assessment. Of the 22,000 protein coding genes and even higher number of genes that code for long intervening non coding RNA (lncRNA) and MicroRNAs [6], several hundred are now implicated in cancer development and progression.

2 Germline and Somatic Variants

Inherited or **germline** genetic variants are present in every cell of the body, including the tumor cells and are studied for evaluating inherited monogenic or polygenic cancer risk or for their pharmacogenomic relevance. The acquired or **somatic** genetic alterations are present only in the cancer cells and are studied to understand genetic mechanisms of cancer and improve diagnostic, prognostic and treatment methods of cancer. Germline variants are present in nearly 50% or 100% sequencing reads in their heterozygous or homozygous states, respectively. However, the allele frequency of somatic variants is highly variable, making it difficult to ascertain their zygosity. This is due to varying admixture of normal and tumor cells in a biopsy sample, variation in the number of clones or subclones of tumor harboring a somatic variant and issues in variant calling through stringent bioinformatics pipelines. Ideally, a variant identified in a tumor sample can be called a true somatic variant only after excluding its germline origin by sequencing normal tissue or blood derived DNA. In absence of this information, any variant identified in a tumor sample with an allele frequency approaching 50% or 100% raises the possibility of this variant being of germline origin and the hereditary implications. Compared to germline variants, confident identification of a somatic variant and its classification is more difficult. This is due to technical issues in sequencing the degraded DNA extracted from old tumor blocs, artifacts, tumor heterogeneity and abundance of uncharacterized passenger somatic variants. For somatic variants, there are specialized and curated databases and guidelines for interpretation and classification but a consensus remains elusive [7].

3 Oncogenes and Tumor Suppressor Genes

Broadly, the cancer-associated genes are classified as proto-oncogenes, which become oncogenes after a gain of function (GoF) mutation, or the tumor suppressor genes (TSG), which promote cancer development if they have a loss of function (LoF) mutation. TSGs such as BRCA1, BRCA2, MLH1, MSH2, etc. are important from the perspective of cancer biology, inherited risk and more recently for precision medicine using synthetic lethality and cancer immunotherapy. Oncogenes such as K-RAS, Her2Neu and EGFR govern aggressiveness of certain tumors and used for biomarkers, molecular profiling, companion diagnostics or therapeutic targets. The major difference between oncogenes and TSGs are shown in Table 1. Mutations in the TSG could either be inherited or acquired but mutations in oncogenes are almost always acquired, with the exceptions being the RET and MET oncogene. The increasing clinical and research-based exome or genome sequencing often identifies structural or

Table 1 Role of oncogenes and tumor suppressor genes

	Oncogenes	Tumor suppressor genes
Examples	Her2Neu, K-RAS, MYC, EGFR, RET, MET, BRAF, etc.	BRCA1, BRCA2, MLH1, MSH2, MSH6, TP53, APC, PALB2, STK11, RB, VHL, TSC, etc.
Major cellular role	Cell signaling that drives cell division or proliferation under specific physiological and pathological conditions	Controls integrity and efficiency of DNA repair, cell division, apoptosis and other housekeeping and homeostasis functions during embryogenesis, growth, differentiation and senescence
How mutations perturb cellular behavior, contribute to hallmarks of cancer	Instead of context dependent and reversible activation, they become constitutively activated due to specific point mutation or overexpression. This promotes sustained proliferation, uncontrolled growth and aggressive cellular phenotype	Instead of maintaining homeostasis, mutations in TSGs cause impaired and inefficient repair of specific types of DNA damage, impaired cell cycle control, apoptosis and reprogramming of energy metabolism
Nature of cancer-causing mutations	Gain-in-Function: Gene amplification with increase in the copy number or a heterozygous missense point mutation at a specific codon results in Gain-in-Function of uncontrolled and sustained multiplication. Usually, it is an acquired somatic mutation but rarely it is an inherited germline mutation (e.g., RET)	Loss-of-Function: Truncating mutations (nonsense or frameshift indels); absence of protein (chromosomal deletion) or an aberrant nonfunctional protein (splice site or certain pathogenic missense mutations). For total loss of a specific tumor suppressor activity, both alleles are inactivated as per Knudson's hypothesis
Role in cancer prevention and precision oncology	Specific mutations and activated oncogenic signaling in tumor used for molecular classification with prognostic and predictive value. Specific driver mutations or amplifications in kinases and other genes can be blocked by small molecule inhibitors (e.g., imatinib) or monoclonal antibodies (e.g., trastuzumab)	Identification of germline pathogenic mutation is used for hereditary cancer risk, extended family testing and cancer prevention. Germline or somatic mutation in DNA damage repair pathways genes predict platinum sensitivity and used in synthetic lethality approach (PARP inhibitors). Germline MMR gene mutations predict response to immunotherapy

functionally relevant genetic alterations in genes that are yet to be classified as oncogenes or TSGs. Genes that harbor protein truncating or splice site mutations in several tumors, are expected to be tumor suppressors, especially if such mutations are seen with loss of heterozygosity (LOH) events in the tumor. In contrast, genes with missense mutations in particular codons or genes showing amplification in several tumors, are likely to be oncogenes. Some genes such as NOTCH1 show a tissue and cellular context dependent role as an oncogene or as a tumor suppressor gene [8]. The TCGA and ICGC consortium projects through whole exome, genome and transcriptome analysis of a large number of diverse human cancers have established the genomic landscape of various human cancers and the mutational signatures of different carcinogenic exposures. These and other studies discovered new driver genes, previously unknown genetic mechanisms such as chromothripsis, and revealed that cancer genomes have four or five driver mutations in the coding and noncoding genomic elements and germline variants also influence the patterns of somatic mutation and tumor evolution [9].

4 Classification and Reporting of Genetic Variants

The sequence in which the four nucleotides, adenine, thymine, guanine and cytosine, are arranged in the genomic DNA is distinct for each life form and unique for every individual within a species. Any nucleotide base in an individual that differs from the reference healthy population genome is a genetic variant. The full spectrum of human genetic diversity is yet to be documented in several non-Caucasian races. Of the hundreds to thousands of genetic variants in each individual, overwhelming majority are polymorphic variants of little or no biological consequence or disease risk. However, some variants that are rare in the population may confer disease susceptibility in individuals with these rare variants. The nucleotide sequence of the region of interest is determined using an appropriate DNA sequencing technology, mapped to the reference sequence derived from normal healthy population and seen whether it is an exact match or has one or more variants. The standardized nomenclature and reporting for DNA and amino acid sequence variants developed by the Human Genome Variation Society (HGVS) helps to develop common genome databases for reproducible genetic analysis and standardized reporting, with minimum risk of false variant interpretation [10]. Variants are classified and interpreted in terms of their effect on the expression of the gene or the structure and function of the protein they code. HGVS recommends DNA genetic variants to be classified as **substitutions** of one nucleotide base with another, **insertion**, **deletion** or insertions with deletions of one or more bases, **duplications**, **inversions**, **repeated sequences** or **complex** variants. The genetic alterations identified in cancer associated genes and their disease risk is described in Table 2.

Genetic alterations are described to indicate their location (chromosome, gene, exon or intron); zygosity (heterozygous or homozygous) and nature (substitution, indel, etc.) using the HGVS nomenclature. Using the prefix “c.” for the coding DNA position and prefix “p.” for the amino acid position, the variant allele is described with its known or predicted effect. Technically, any genetic variant is a mutation but the term mutation has a connotation for disease risk. To avoid misinterpretation, all alterations should be called ‘variants’ along with a description of their likely pathogenicity, and not as ‘mutations’. The five-tier variant classification system proposed by the International Association for Research in Cancer (IARC) [11] and adapted by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP), recommends that all variants should be described as either (1) benign; (2) likely benign; (3) uncertain significance; (4) likely pathogenic; or (5) pathogenic [12]. It is based on evidence from population, computational and functional data available in freely accessible disease and population databases like dbSNP, HGVS, 1000 Genome, gnomAD, Leiden Open Variation Database (LOVD) and ClinVar which archives reported human variants with disease associations and supporting evidence [13]. The ACMG, AMP and the International Society for Gastrointestinal Hereditary Tumors (InSiGHT) [14] use the following five classes of genetic variants:

Pathogenic (class 5) or likely pathogenic (class 4) variants: These variants significantly alter the gene and coded protein and are known or predicted to cause cancer. With the rare exception of Ashkenazi Jews and some inbred populations with a 1–2% population frequency of class 5 founder mutations, pathogenic germline variants are very rare in normal population. The converse is not true and every rare allele with population frequency of <1% or < 0.1% may not be pathogenic.

Variant of uncertain clinical significance VUS (class 3): A missense or inframe indel variant is considered as VUS if it is rare or absent in the reference normal population and comprehensive studies to evaluate its pathogenicity are either not available or inconclusive. Due to major differences in the genetic constitution between different races and communities, a missense alteration which may be a polymorphic variant in a less studied population, may be very rare or absent in another population used as reference. Thus, a polymorphic benign MLH1 gene variant present in 4% healthy individuals from a particular Indian community, may be very rare or absent in the wider Indian or Caucasian reference genome. In absence of this knowledge, it will be reported as a VUS.

Benign (class 1) or likely benign (class 2): These are deep intronic, synonymous or missense polymorphic variants, often present in >1% of healthy individuals.

Table 2 Type of genetic alterations and their effect

Genetic alteration	Effect on coded protein or gene expression	Biological role in cancer	
		Germline variants	Somatic variants
Base substitution in deep intronic or intergenic	No effect. Rarely, it may introduce a cryptic splice site or alter gene expression	SNPs with no or very mild modulatory effect in some cancers Very rarely pathogenic	No effect
Base substitution in 5′ or 3′ UTR	Usually no effect Sometimes may alter UTR regulatory elements	SNPs with no or very mild modulatory effect in some cancers. Rarely pathogenic[a]	No effect
Base substitution in coding exonic region	Codes same AA (synonymous or silent)	SNPs with no or very mild modulatory effect in some cancers. Very rarely pathogenic[a]	No effect
	Codes different AA (missense variant). Protein structure or function may or may not change	SNPs with no or very mild modulatory effect or pharmacogenomic relevance Pathogenic in specific codons of oncogenes RET and MET (GoF) or few TSGs, e.g., TP53 (LoF)	In oncogenes, GoF variants in specific codons are driver and targetable, e.g., BRAFV600E In TSGs, most are passenger but few are LoF pathogenic variants
	Codes for Stop codon (stopgain or Nonsense), causing truncated protein	In TSGs almost always pathogenic	In TSGs usually pathogenic
	Abolishes Stop codon (stoploss) causing exon retention	In TSGs almost always pathogenic	In TSGs usually pathogenic
Base substitution in essential splice site	Aberrant splicing and aberrant protein due to retention/deletion of exon/intron	In TSGs almost always pathogenic	In TSGs usually pathogenic
Small insertion or deletion in exons	In-frame insertion or deletion adds or removes 1 or 2 AA	Usually, polymorphisms with no or mild modulatory effect. Rarely pathogenic[a]	No effect
	Frameshift insertion/deletions introduces stop codon with truncated protein	Almost always pathogenic	In TSGs usually pathogenic
Large genomic rearrangement (LGR)	Deletion/duplication of exons/introns with aberrant protein	Almost always pathogenic	In TSGs usually pathogenic
Chromosomal abnormalities or structural variants	Deletions, duplications or translocation of chromosomes cause gain or loss of function of genes or oncogenic fusion products	These are rare in germline and cause congenital syndromes, some with increased cancer risk	Common driver mutations in hematological malignancies and some solid tumors or cause the second hit in TSGs by LOH

UTR untranslated region, *LOH* loss of heterozygosity

[a] Type of mutations which are rarely pathogenic, should be interpreted as likely pathogenic based on multiple lines of evidence, including family studies and functional studies

5 Hereditary Cancer Syndromes

Germline pathogenic or likely pathogenic mutation in cancer susceptibility genes results in a high lifetime risk of developing certain cancers. Over 30 well characterized hereditary cancer syndromes and their variants are known. Barring a few Mendelian recessive syndromes such as xeroderma pigmentosum (XP), constitutional mismatch repair deficiency (CMMRD), MYH-associated polyposis or Fanconi's anemia, all others have a Mendelian dominant pattern of inheritance with a 50:50 chance of passing on the gene mutation and cancer risk to the offspring. While few phenotypic manifestations are unique to a particular gene or syndrome, e.g., carpet of adenomatous polyps in APC mutation or MEN2B phenotype in RET gene mutation, most benign and malignant manifestations are shared between different syndromes and genes. With wider use of genetic testing, it has been established that classical syndromic features of HBOC or Lynch syndrome are uncommon in carriers of BRCA or MMR gene mutation and their families. This is explained by incomplete penetrance, incomplete or unreliable family history and heterogeneity in clinical manifestations. The genetic counseling and testing advice is therefore based on the differential diagnosis of possible hereditary cancer syndromes.

5.1 Universal Features of Hereditary Cancers and the Knudson's Two-Hit Hypothesis

The hereditary form of retinoblastoma (RB) and its bilateral presentation was known long before the underlying genetic mechanism was known. Alfred Knudson in a seminal 1971 paper titled "Mutation and Cancer: Statistical

Study of Retinoblastoma" proposed that two genetic hits are required for retinoblastoma development. Using a semilogarithmic plot of fraction of bilateral and unilateral cases not yet diagnosed with RB against age in months, he derived that the straight line of hereditary RB and curved line of sporadic RB could only be explained by two genetic hits or mutation required for the development of RB. In hereditary RB, all retinal cells must have the first hit at birth and subsequently may have acquired the second hit in one or more retinal cells of one or both eyes. In the sporadic or nonhereditary RB, two successive genetic hits or mutation were acquired after birth in one of the retinal cell. Clonal proliferation of a transformed retinal cell with two hits of the responsible gene (RB1) resulted in the development of the retinoblastoma tumor. This was a major advancement in our understanding of the effect of germline and somatic mutations in one or both alleles of the same gene and later shown as the key feature of how tumor suppressor genes cause cancer with the second copy of the TSG lost through deletion or other mechanisms and causing LOH. The relevance of this genetic model (Fig. 1) of a person born with the first genetic hit (heterozygous germline mutation) and subsequently acquiring the second hit (somatic mutation) later in life explains three key universal features of hereditary cancers.

- High lifetime cancer risk in those born with the one mutated allele (germline first hit).

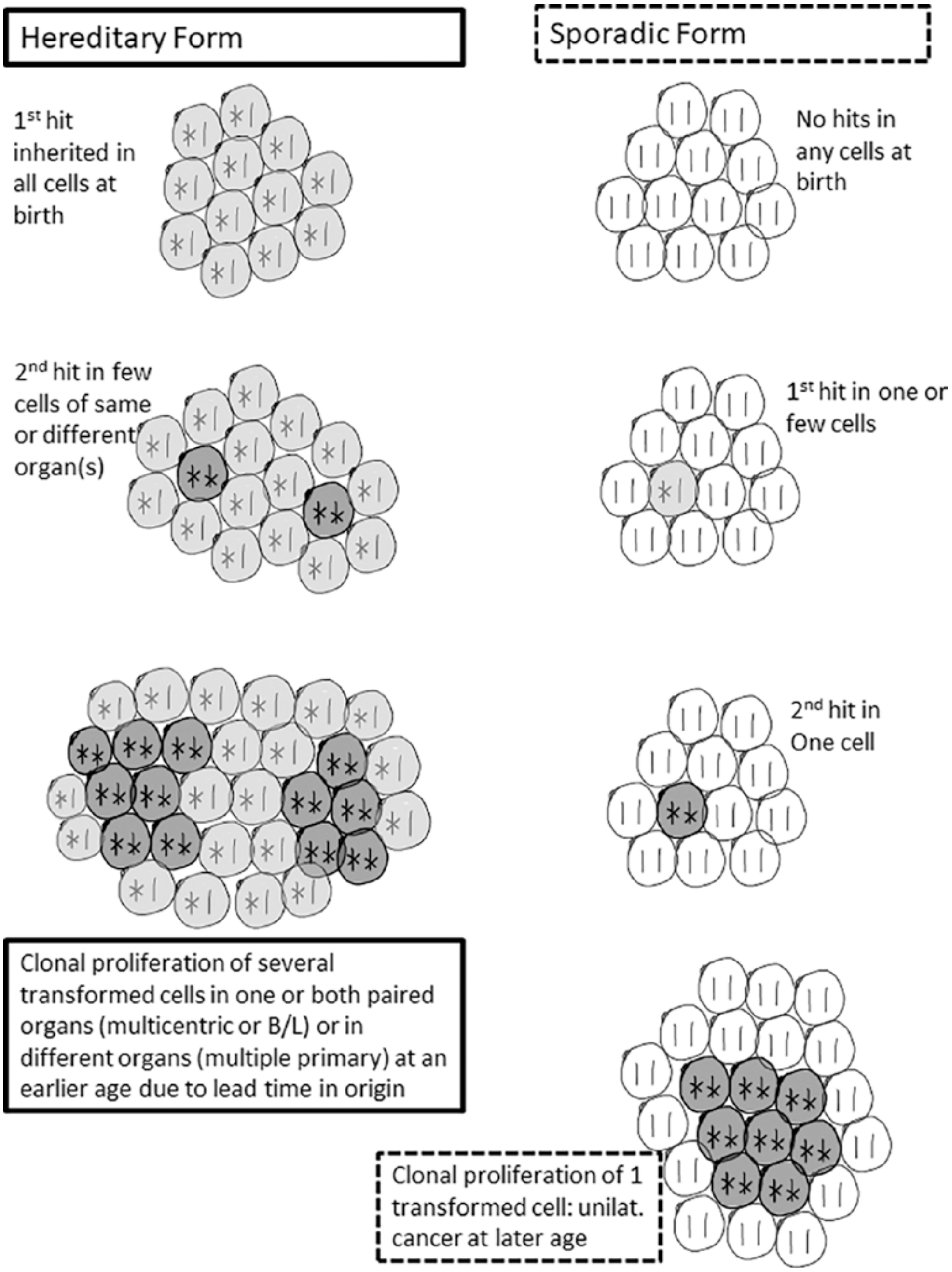

Hereditary Form
1st hit inherited in all cells at birth
2nd hit in few cells of same or different organ(s)
Clonal proliferation of several transformed cells in one or both paired organs (multicentric or B/L) or in different organs (multiple primary) at an earlier age due to lead time in origin
Sporadic Form
No hits in any cells at birth
1st hit in one or few cells
2nd hit in One cell
Clonal proliferation of 1 transformed cell: unilat. cancer at later age

Fig. 1 Knudson's two-hit model and clinical features of hereditary cancer

- Earlier age at diagnosis in hereditary cancers as compared to their sporadic counterparts.
- Significantly higher incidence of bilateral, multiple primary or multifocal cancers.

5.2 Specific Features of Hereditary Cancer Syndromes

Each hereditary cancer syndrome is defined based on the combination of characteristic features in terms of mode of inheritance, specific cancer types, histological features, age at cancer diagnosis and certain cutaneous, ocular, endoscopic or radiological features. While germline mutation is present in every cell, tissue differences in gene expression and the function of that gene may increase cancer risk in few but not all organs and explain the syndromic manifestations. Dermatological, facial, ocular, endoscopic or imaging findings indicative of an underlying gene mutation are present only in a few syndromes (Table 3). For majority of the common cancer predisposition syndromes, the only clue is a significant family history or personal history of early onset or bilateral cancer, sometimes with specific tumor or molecular characteristics. Some cancers with specific histological features (Table 4) or certain phenotypic features (Table 3) are highly suggestive of a particular syndrome with a specific genetic basis. This should alert the pathologist and clinician to look for other features of that syndrome and consider appropriate genetic evaluation and germline testing.

It is important to note that cancers in some organs like breast, kidney, stomach, pancreas or brain can occur in many hereditary cancer syndromes, sometimes with syndrome specific differences in molecular or histological subtype. Breast cancer is a prominent feature not only of the HBOC syndrome but also of LFS, PJS, Cowden and HDGC syndrome and a less prominent but increasingly recognized feature of Lynch and NF1 syndromes. Knowledge regarding age at breast cancer diagnosis and its receptor status or other cancers and phenotypic features in different hereditary cancer syndromes as shown in Table 5 could guide appropriate genetic testing and risk management.

Autosomal recessive inheritance is very rare and due to homozygous or bi-allelic mutation usually inherited from consanguineous parents or from inbred community. These syndromes include:

Ataxia Telangiectasia (*ATM gene):* Presents with conjunctival telangiectasia, ataxia, immunosuppression and extreme radiosensitivity with 25% risk of hematolymphoid malignancy [17].

Fanconi Anemia (BRCA2 or 21 other FANC family genes): All are autosomal recessive except the X linked FANCB and the autosomal dominant FANCR. It is commonly associated with congenital anomalies and 70 cases have bone marrow failure, 50% have myelodysplastic syndrome, 5% develop acute leukemia and 20% develop head neck, female genital or and anal squamous carcinomas [49].

Constitutive Mismatch Repair Deficiency (CMMRD) Syndrome (MMR genes, most commonly PMS2): Café-au-lait spots with very high risk of CNS, GI and acute leukemias [50].

MUTYH-Associated Polyposis (MAP) Syndrome (MYH gene): Adenomatous with or without serrated or hyperplastic colorectal polyps which are not as profuse as in FAP and have 80% colorectal cancer risk [15, 16, 51].

Xeroderma Pigmentosum (8 genes, XP-A to XP-G and XP-V): Presents with extremely sun-sensitive dry pigmented atrophic skin and lentigines, >90% cases develop squamous or basal cell carcinoma or melanoma over the sun exposed skin, eyelids, conjunctiva or sometimes over the tip of the tongue. Cognitive impairment is seen in 25% cases [52].

Bloom Syndrome (BLM gene coding for RecQ helicase): Presents with skin erythema, telangiectasia, short stature, endocrine and immune deficiency and 80% risk of hematolymphoid, GI, head neck or other malignancy by age 40 years [53].

Autosomal-dominant inheritance due to heterozygous mutation include all common and some rare hereditary cancer syndromes such as HBOC, Lynch, MEN, LFS, RB, PJS, NF1, etc. listed in Table 3.

Age at cancer diagnosis varies in different syndromes, as shown for breast cancer in Table 5. Even for the same gene, the age at diagnosis could vary for different cancers. For example, in BRCA2 mutation carriers, the risk for female breast cancer starts in the early twenties, while the risk for ovarian and prostate cancer starts in the late 30s and 40s, respectively. This information is used in deciding the age at which genetic testing should be done and cancer screening should be initiated and counseling about prenatal or preimplantation genetic diagnosis. Syndromes can be broadly classified as

- **Predominantly childhood cancer predisposition syndromes:** Hereditary retinoblastoma, Wilm's tumor/WAGR syndrome, Fanconi anemia, CMMRD, juvenile polyposis syndrome.
- **Childhood and adult-onset cancer predisposition:** Li–Fraumeni syndrome, MEN2 syndrome, NF1, tuberous sclerosis, XP.
- **Predominantly adult-onset cancer predisposition syndromes:** HBOC, Lynch, FAP, Cowden, Peutz–Jeghers, HDGC, hereditary renal cancers, etc.

Sex differences in cancer predisposition is common in HBOC associated BRCA1, BRCA2, CHEK2, RAD51 and PALB2 genes with the breast or ovary cancer risk being much higher in women as compared to breast or prostate cancer risk in men. The only gene with predominantly male cancer predisposition is HOXB3 with ~35% prostate cancer risk. For MMR, NF1, NF2, APC, RET, RB and few other genes, no major sex differences in cancer risk are observed.

Table 3 Syndromic features and cumulative lifetime risk for specific cancers in mutation carriers (rounded off to nearest 5%/10%)

GENE (Syndrome)	Syndromic phenotypic feature or any benign tumors	Breast	Colorectal	CNS	Endometrial	Gastric	Kidney/Ureter	Ovary	Pancreas	Prostate	Skin	Thyroid	
APC[d] [15, 16] (FAP, Turcot–Gardner)	Extensive adenomatous polyps, osteoma, CHRPE desmoid fibromatosis		95%	5% Medullo		10%				[e]		15% PTC	5% HPB, periampullary or duodenal
ATM[d] [17]	Not in heterozygotes	30%								[e]			Lung[e]
BLM [18]	None	40%											
BMPR1A [19] (Juvenile polyposis synd)	Juvenile hamartomatous or adenomatous polyps in GI (5–100)		40%			[e]							Small bowel[e]
BRCA1[a] [20–23] (HBOC synd)	None	70%						45%	[e]	[e]			Breast cancers usually TNBC
BRCA2[a,d] [20–23] (HBOC synd)	None	70%						30%	10%	15%			Breast cancers usually ER +ve
BRIP1[a] [18, 24]	None	15%						5%					
CDH1 [25] (HDGC synd)	Orofacial cleft	45%				40%							Invasive lobular ca
CHEK2[a] [22, 26]	None	25%								[e]			
FH [27] (HLRCC)	Uterine and cutaneous leiomyoma						RCC-O RCC-Ch						
FLCN [27] (Birt–Hogg–Dubé synd)	Skin fibrofolliculomas, angiofibroma, lung cysts, pneumothorax						RCC-HOCT RCC-P Oncocytoma						
HOXB13 [28]	None									35%			
MEN1 [29] (MEN1 synd)	Pituitary or parathyroid adenoma, NET			40% pituitary		40% NET			70% NET			80% PTh	ACC 40%
MET [27, 30] (HPRC synd)	None						RCC-P1						
MLH1[b] [31] (Lynch synd)	Keratoacanthoma	10%	45%	[e]	45%	5%	10%	10%	5%	15%	5%		HPB 5%
MSH2[b] [31] (Lynch synd)	Keratoacanthoma	15%	45%	5%	60%	[e]	25%	15%	[e]	30%	5%		
MSH6[b] [31] (Lynch synd)	Keratoacanthoma	15%	15%	[e]	45%	[e]	10%	15%	[e]	20%			
NF1[c] [32] (Neurofibroma-tosis type 1)	Neurofibromas, CAL, axillary freckles, Lisch nodule, cognitive defect, plexiform neurofibroma	[e]		25%									MPNST 10%, RMS 5%
NF2[c] [33] (Neurofibromato-sis type 2)	Hearing loss, cataract, Schwannoma, skin lesions, meningioma			95%									Bilat vestibular schwannoma >90%
PALB2[a] [34]	None	35%							[e]	[e]			
PMS2[b, d] [31, 35] (Lynch synd)	None	[e]	15%		15%								

(continued)

Table 3 (continued)

GENE (Syndrome)	Syndromic phenotypic feature or any benign tumors	Breast	Colorectal	CNS	Endometrial	Gastric	Kidney/Ureter	Ovary	Pancreas	Prostate	Skin	Thyroid	
PTEN[c] [36] (Cowden or PTEN hamartoma synd)	FT, COP, PPK, macrocephaly penile freckles, GI hamartomas, LDD/CDG, thyroiditis	70%	20%		20%		10–30% RCC-CC				5%	25%	Lung cancer[e]
RAD50[a] [18]	None	30%											
RAD51-C/D[a] [37]	None	20%						10%					
RB1[d] [38, 39] (hereditary RB)	Dysmorphic features with large deletions in 13q			5% pineal									RB >90%, sarcoma 5%
RET[d] [40] (MEN2A)	Parathyroid hyperplasia											50–100%	PCC 5–25%
RET[d] [40] (MEN2B)	Marfanoid habitus, tongue and lip neurinomas, blubbery lips											100%	PCC 50%
SDHB/C/D [41, 42] (hereditary PGL/PCC)	Paraganglioma						RCC-O RCC-Ch RCC-CC						PGL or PCC 50–60%
SMAD4 [19] (Juvenile polyposis syndrome)	Juvenile hamartomatous or adenomatous polyps, (5–100), HT, connective tissue disorder		40%			[e]							Small bowel[e]
STK11 [43, 44] (Peutz–Jeghers synd)	Lip / oral pigmentation; hamartomatous GI polyps, SCTAT	55%	40%		10%	30%		20%	30%				
TP53 [45] (Li–Fraumeni syndrome)	None	85%	5%	25%			[e]	[e]	[e]	[e]	[e]		Sarcoma 50%, ACC 5%, lung[e]
TSC1/2[c] [46] (tuberous sclerosis)	Facial angiofibromas, shagreen patches. SEN, cortical tubers Lung, eye, heart, renal hamartoma			20% SEGA									
VHL[c] [47] (VHL disease)	Retinal angiomas, renal and pancreatic cysts, NET			80% HB			70% RCC-CC						PCC, inner ear ELST
Rare syndromes (CDKN2A PTCH, WT1) [48]				Medullo (Gorlins)			Wilm's tumor (WAGR)				BCC MM		

ACC adreno-cortical carcinoma, *BCC* basal cell carcinoma, *CHRPE* congenital hypertrophy of retinal pigment epithelium, *COP* cobblestone oral papules, *CAL* café au lait spots, *ELST* endolymphatic sac tumors, *FH* fumarate hydratase, *FT* facial trichilemmoma, *HB* hemangioblastoma, *HBOC* hereditary breast ovarian cancer, *HPRC* hereditary papillary renal carcinoma, *HT* hemorrhagic telangiectasia, *LAM* lymphangioleiomyomatosis, *LDD/CDG* Lhermitte–Duclos disease or cerebellar dysplastic gangliocytoma, *MEN* multiple endocrine neoplasia, *MM* malignant melanoma, *MPNST* malignant peripheral nerve sheath tumor, *NET* neuroendocrine tumors, *PCC* pheochromocytoma, *PPK* palmo-plantar keratosis, *PTh* parathyroid, *PTHS* PTEN hamartoma syndrome, *RB* retinoblastoma, *RCC* renal cell carcinoma, *RCC-CC* clear cell, *RCC-Ch* chromophobe, *RCC-P* papillary, *RCC-O* oncocytic, *RCC-HOCT* hybrid oncocytoma chromophobe tumor, *RMS* rhabdomyosarcoma, *SCTAT* sex cord tumor with annular tubules, *SDH B/C/D* succinate dehydrogenase subunits B, C, D, *SEN* subependymal nodules, *SLE* systemic lupus erythematosus, *VHL* von Hippel–Lindau's disease

[a] BRCA1/2 and its interacting genes

[b] Mismatch repair genes and its interacting genes

[c] Phakomatosis/neurocutaneous syndromes

[d] Genes with major phenotypic or penetrance difference depending on mutation location and zygosity

[e] Risk higher than population risk but not very high risk

Table 4 Cancer types highly suggestive of a syndrome

Cancer type specific to a syndrome/ gene	Syndrome (gene)
Hypodiploid acute lymphoblastic leukemia	Li–Fraumeni syndrome (*TP53*)
Choroid plexus tumor or carcinoma	
Acoustic neuroma (often bilateral)	NF2 syndrome (*NF2*)
Optic pathway glioma	NF1 syndrome (*NF1*)
Malignant peripheral nerve sheath tumor	
Cerebellar or spinal hemangioblastoma	Von Hippel–Lindau's disease (*VHL*)
Subependymal giant cell astrocytoma (SGCA)	Tuberous sclerosis (*TSC1/ TSC2*)
Retinoblastoma—multicentric or bilateral	Hereditary retinoblastoma (*RB1*)
Multiple basal cell carcinoma	Gorlin's syndrome (PTCH1)
Medullary thyroid cancer	MEN type 2 (*RET*)
Diffuse gastric cancer	Hereditary diffuse gastric cancer (*CDH1*)
Renal cancer—Hybrid oncocytoma and chromophobe	Birt–Hogg–Dube syndrome (*FLCN1*)
Renal cancer—Papillary type 1	Hereditary papillary renal cell cancer (*MET*)
Renal cancer—Papillary type 2	Hereditary leiomyomatosis and renal cell cancer (*FH*)
Microsatellite unstable or MSI high colorectal or endometrial carcinoma	Lynch syndrome (heterozygous MMR genes)

Penetrance, cumulative cancer risk and genotype–phenotype correlation are the most important considerations in counseling families. Penetrance refers to the proportion of individuals with phenotypic manifestation of the underlying genotype in terms of cancer development and syndrome specific phenotypic features such as polyps, facial appearance, eye or skin signs (see Table 3). Age and gender specific cumulative risk of a particular cancer in confirmed mutation carriers of a gene is the most useful in clinical practice. Few syndromes such as FAP and MEN2B have a near complete penetrance, both for syndromic phenotypic features and cancer development. The common hereditary cancer syndromes such as HBOC, Lynch, LFS, RB, etc. with high penetrance gene mutations have a cumulative cancer risk of 50–95%. Heterozygous mutations in ATM, BARD1, BLM, BRIP1, CHEK2, HOXB13, NBN, PALB2, PMS2, RAD50, RAD51 and a few others have an intermediate or moderate penetrance with cumulative cancer risk between 20 and 50% (see Table 3). The penetrance and phenotype associated with mutations in certain genes can be greatly affected by the location of the mutation within the genes. Mutations in certain regions of the APC gene cause the attenuated form of FAP or carry significantly higher risk for desmoid tumors [15]. Similarly RET gene mutation at 918 codon (M918T) produce classical MEN2B phenotype and childhood medullary thyroid cancer (MTC), while codon 634 (C634R) produce MEN2A with adult onset MTC in absence of MEN2B phenotypic features [40]. Of the four MMR genes, extracolonic cancers in general and skin cancers in particular

Table 5 Inherited breast cancer risk in different syndromes

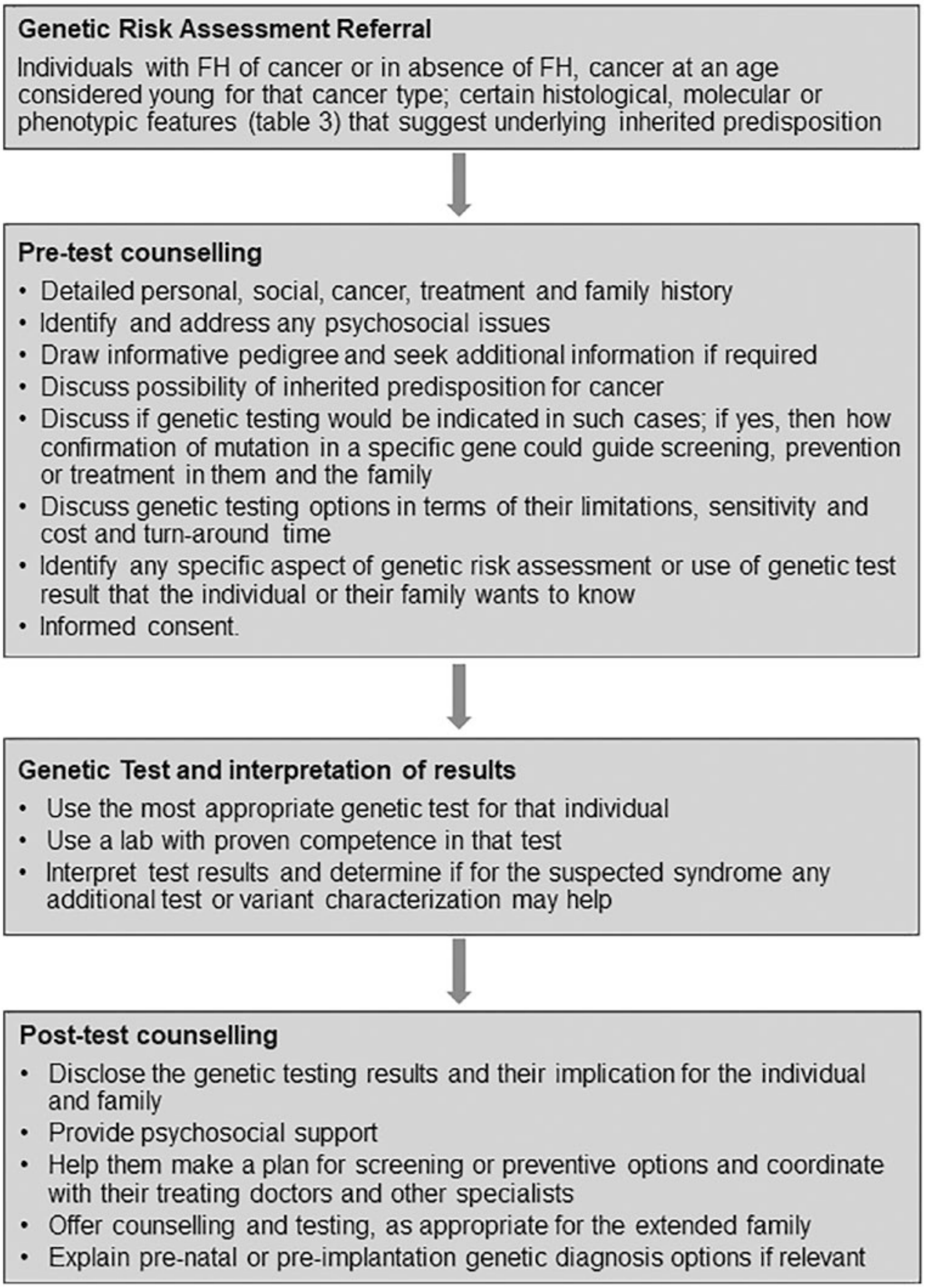
Syndrome (*Gene*) [Ref]	Cancer risk			Age at breast cancer diagnosis	Receptor status	Phenotypic features
	Breast	Ovary	Others			
HBOC (*BRCA1*) [20–23]	+++++	+++	+/–	Early onset	IDC TNBC	No
HBOC (*BRCA2*) [20–23]	++++	++	+ Pancreas, Prostate	Early and late onset	IDC ER+ve Her2−ve	No
HBOC (*ATM, PALB2, RAD51*) [18, 34, 37]	++	+/–		Early and late onset	Not described	No
LFS/LFL (*TP53*) [45]	++++	+	++++	Very early onset	IDC ER+/– Her2+	No
PJS (*STK11*) [43, 44]	++	+	++ GI	Early onset	IDC ER+ve Her2−ve	Pigmentation and polyps (see Table 4)
Cowden (*PTEN*) [36]	++			Early onset	Not described	Cutaneous (see Table 4)
Lynch (*MMR*) [31]	+	+	++++ GI, uterus GU, brain, skin	Early onset	Not described	No
NF1 (*NF1*) [32]	+	–	CNS	Early and late onset	IDC ER+/– Her2+	Cutaneous, skeletal, CNS (see Table 4)
HDGC (*CDH1*) [25]	+++	–	++++ Diffuse gastric cancer	Early onset	Lobular carcinoma	No

GI gastrointestinal, *GU* genitourinary, *IDC* infiltrating duct carcinoma, *CNS* central nervous system, *TNBC* triple negative breast cancer are far commoner in MSH2 as compared to MLH1, MSH6 and PMS2 while the cumulative cancer risk is significantly lower in PMS2 gene mutation.

6 Genetic Risk Assessment and Genetic Counseling

Genetic risk assessment is the process of suspecting and confirming inherited predisposition to cancer through genetic counseling, pedigree analysis and germline genetic testing when indicated. The treating oncologist, pathologist or radiologist refers for genetic risk assessment if based on personal and family history of cancer, or certain histological, radiological or phenotypic features, they suspect inherited cancer predisposition. Inherited cancer risk is confirmed through appropriate germline genetic testing which is preceded by **pretest genetic counseling** and followed by **posttest genetic counseling** (Fig. 2).

Genetic counseling, especially for cases with significant family history or a known mutation, should preferably be imparted through specialized genetics clinics by clinicians or counselors with knowledge and experience in various aspects of hereditary cancers including the utility or limitations of



Genetic Risk Assessment Referral

Individuals with FH of cancer or in absence of FH, cancer at an age considered young for that cancer type; certain histological, molecular or phenotypic features (table 3) that suggest underlying inherited predisposition

Pre-test counselling

- Detailed personal, social, cancer, treatment and family history
- Identify and address any psychosocial issues
- Draw informative pedigree and seek additional information if required
- Discuss possibility of inherited predisposition for cancer
- Discuss if genetic testing would be indicated in such cases; if yes, then how confirmation of mutation in a specific gene could guide screening, prevention or treatment in them and the family
- Discuss genetic testing options in terms of their limitations, sensitivity and cost and turn-around time
- Identify any specific aspect of genetic risk assessment or use of genetic test result that the individual or their family wants to know
- Informed consent.

Genetic Test and interpretation of results

- Use the most appropriate genetic test for that individual
- Use a lab with proven competence in that test
- Interpret test results and determine if for the suspected syndrome any additional test or variant characterization may help

Post-test counselling

- Disclose the genetic testing results and their implication for the individual and family
- Provide psychosocial support
- Help them make a plan for screening or preventive options and coordinate with their treating doctors and other specialists
- Offer counselling and testing, as appropriate for the extended family
- Explain pre-natal or pre-implantation genetic diagnosis options if relevant

Fig. 2 Genetic risk assessment: referral, genetic counseling and genetic testing

various genetic testing and cancer prevention methods and the associated ethical, legal and social issues (ELSI). Families with hereditary cancers face a range of ethical and socio-cultural issues which may be accentuated with genetic testing and should be addressed during genetic counseling. Guilt of passing the cancer risk to children is not uncommon. Outside Europe and North America, most countries do not have mechanisms and specific legislation for protection against genetic discrimination at work place or insurance. Adherence to the principles of genetic counseling helps in minimizing the psycho-social impact of hereditary cancer risk and genetic test results on an individual or a family. These include autonomy, empathy, beneficence, nonmaleficence, nondirectiveness and informed decision making while maintaining confidentiality and privacy. The informed consent or assent should include all these aspects. Some individuals may require referral for specialized psychological counseling.

A detailed and informative pedigree using standard symbols and methods with details of any phenotypic manifestations and cancers in the family is the most important tool in making syndromic differential diagnosis, estimating the likelihood of inherited predisposition and the genetic testing that may be useful. Medical records and details of cancers in the family are often not available in developing countries and verbal autopsy techniques are heavily relied upon to ascertain the most probable cause of death or type of cancers in the family. For example, ovarian cancer which is the syndrome defining cancer in HBOC is frequently misreported as "abdominal," "stomach," or "uterus" cancer by the relatives. History of recurrent ascites or bloated abdomen with or without cachexia in the last stages of a woman known to have died of cancer is suggestive of terminal ovarian cancer.

7 Germline Genetic Testing

Traditionally, genetic testing was recommended if there was a strong family history or the probability of germline mutation was predicted to be >10% by online tools such as BOADICEA (http://ccge.medschl.cam.ac.uk/boadicea/), BRCAPro or MMRPro (http://astor.som.jhmi.edu/BayesMendel/). This threshold is not strictly applied now with increasing identification of mutations in individuals who do not fit the traditional genetic testing criteria; germline genetic testing being done to identify individuals who may benefit with precision medicine approaches; and the wider availability of germline genetic testing. Genetic testing options are provided to individuals with a reasonable prospect of harboring germline mutation in a moderate to high penetrance gene. In patients with recurrent or refractory breast, ovary, prostate, pancreatic, GI or GU cancers, germline genetic testing is being increasingly done to identify germline mutation in BRCA1, BRCA2 or other DNA damage repair pathway genes to predict sensitivity to platinum agents or PARP inhibitors or in the MMR pathway genes that predict benefit with immunotherapy.

During genetic counseling, individuals are helped to make an informed decision and provide consent based on the availability and access to a genetic test, its cost, turnaround time and need for additional testing if the test results are negative. When **Sanger sequencing** was the only available method, one or two major syndrome associated genes were sequenced with or without large genomic rearrangement (LGR) analysis. With wider availability and decreasing cost of **multigene germline NGS panels,** the current practice is as follows:

- NGS germline panel testing of 8–100 genes is the default option for majority of cases.
- In cases with characteristic syndromic features of FAP, MEN2, NF1, PJS, etc., sequencing (+/− LGR analysis) of a single gene may be considered if it is cost-effective.
- For classical HBOC or Lynch syndrome, if multigene NGS panel is not feasible or significant psychosocial sequelae with VUS identification is expected in an individual, 1–2 most commonly implicated genes may be sequenced (+/− LGR analysis). In Lynch syndrome, gene/s showing loss of expression in tumor on IHC can be tested.
- Individuals from specific communities with a known founder mutation can be first tested for it before more comprehensive genetic testing, as is done in Ashkenazi Jews.

Genetic testing in a family should start with the person who has the characteristic early onset cancer of the suspected syndrome. If a mutation is identified, relatives at risk are offered testing. In families with suspected hereditary cancer syndrome and no person affected by cancer is alive or available for genetic testing, healthy at-risk relatives can be tested if they wish to know their inherited cancer risk.

Sample for genetic testing: Germline mutation analysis is done on genomic DNA from normal cells, preferably peripheral blood lymphocytes (PBL). Cells from buccal swab or scrapings as well as skin biopsy can also be used. After informed consent, 3–6 mL blood sample is collected in EDTA tubes and transported to the laboratory at room temperature. As mutation in DNA from blood sample of a leukemia patient may have somatic origin, germline testing should be done on buccal swab sample.

Genetic testing and reporting: Known sources of preanalytical and analytical errors should be minimized using standard operating procedures and stringent quality assurance and quality control measures. Possibilities of sample mix up within and between families tested together, or their incorrect identification while interpreting results or reporting should be eliminated. If there is slightest of doubt, results should be confirmed on an independent sample. DNA quality should be acceptable for the sequencing method. In Sanger sequencing, the coding region of the gene/s is PCR amplified with specific primers, the amplified DNA is cleaned of impurities, sequenced on automated capillary sequencers using dideoxy-chain termination method. The output of the sequenced region is in the form of chromatogram. With NGS based multigene panel testing, the genomic DNA is fragmented, the region of interest of the genes in the panel is enriched or captured with various methods, amplified and then sequenced using Illumina or other NGS platforms. The raw data generated is checked for quality and special bioinformatic algorithms are used for data interpretation and variant calling. Any variant identified in the sample is compared with existing databases and ClinVar to ascertain is pathogenicity and reported using the five-tier system, using the HGVS nomenclature as described earlier [10, 12, 13]. Benign or likely benign variants are not reported and any pathogenic or likely pathogenic variant identified is reported, with brief explanation of why it is considered pathogenic, and its association with caners in the tested individual and their family. Extended family testing is offered and cancer prevention measures are recommended in mutation carriers. VUS reporting practices are very variable with few laboratories not reporting any identified VUS, some reporting VUS only for the genes implicated in the suspected syndrome, while others report all VUS in the genes included in the panel. Periodic or continuous variant reclassification program should be done by the testing laboratory and the referring clinician should be informed whenever a previously reported VUS has been reclassified as likely benign or pathogenic.

8 Cancer Screening and Prevention

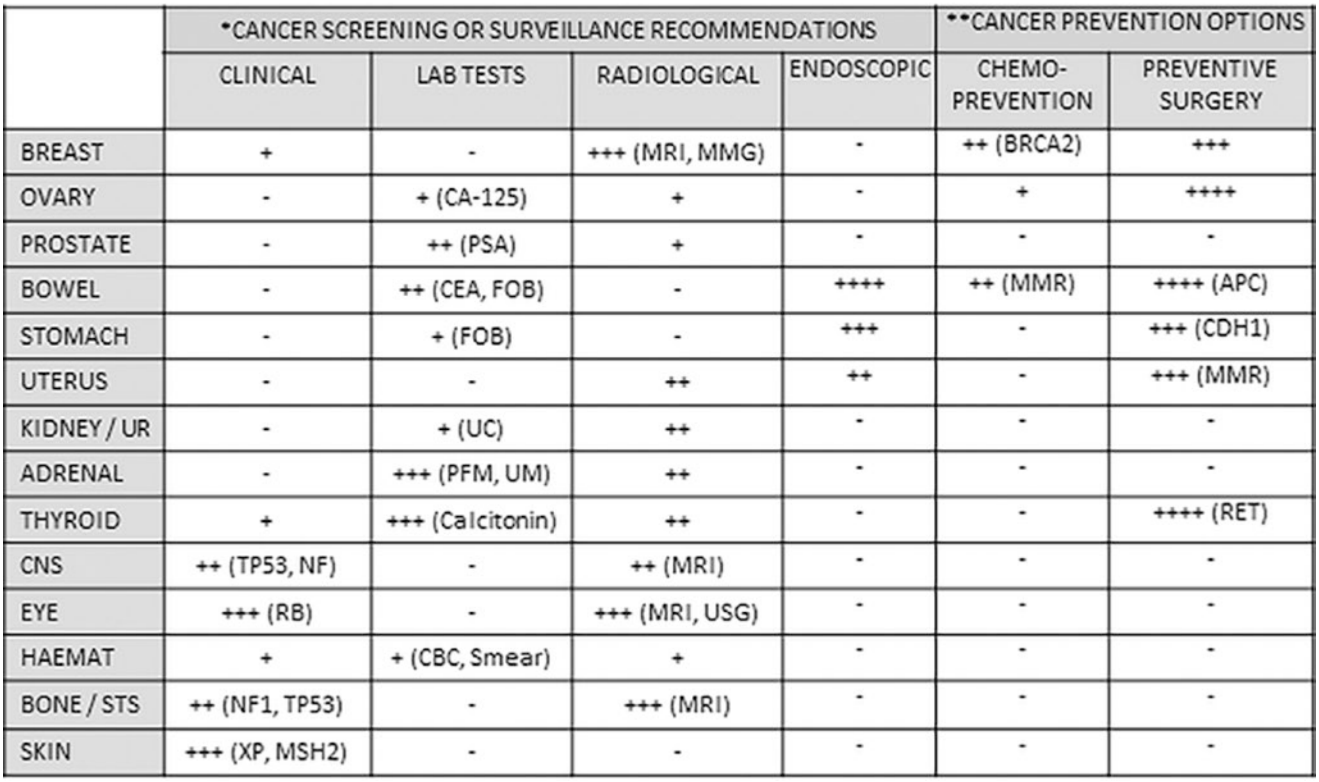
Cancer genetics programs aim to reduce cancer morbidity and mortality in cancer prone families by genetic counseling, genetic testing and cancer prevention and screening advice to mutation carriers. As large cohorts of healthy carriers of specific gene mutation carriers have not been followed up for decades, level 1 evidence for survival benefit with most of the screening and prevention methods is not available. These recommendations by the NCCN, ASCO and other professional societies are therefore based on:

1. Age and gender specific cumulative risk for a cancer in mutation carriers (Table 3) to ascertain if the risk is high enough to institute high-risk screening and prevention from a certain age.
2. Sensitivity and specificity of various clinical, endoscopic, radiological or biochemical methods for early detection of the syndrome associated cancers.
3. Effectiveness, toxicity, acceptability, cost and compliance of nonsurgical and surgical methods for cancer prevention, ideally with long term data on all-cause mortality and quality of life.

Surveillance or high-risk screening for cancer risk in various organs has been previously described [54, 55] and summarized in Fig. 3. Clinical examination can detect early cancers and precancers of the skin and compliment radiological or biochemical evaluation of thyroid, breast, CNS and bone soft tissue tumors. Radiological evaluation with MRI, CT, USG, Mammogram, as appropriate, is useful for screening for breast, CNS, bone soft tissue, prostate and intra-abdominal tumors, but is of limited value in ovarian cancers. Laboratory tests with tumor markers like PSA, calcitonin, plasma free and urinary metanephrines, fecal occult blood and few other tests are useful for screening of some cancers (see Fig. 3). Endoscopy is the main screening method for lower and upper GI cancers. The age for initiating screening and the combination and frequency of screening methods is based on the age specific cumulative risk of a cancer, its natural rate of progression and how different diagnostic methods complement each other.

Chemoprevention using tamoxifen, raloxifene or aromatase inhibitors can almost halve the risk of BRCA2 associated ER+ breast cancer [56] but its use remains low due to some uncertainty regarding the risk benefit ratio with its long-term use. The chemoprotective effect of high-dose aspirin (600 mg daily) for colorectal cancers in Lynch syndrome has been clearly demonstrated in the CAPP2 randomized trial [57], but it is not routinely used, with the CAPP3 trial yet to report whether lower doses would also be chemo-preventive.

Risk-reducing surgeries for specific cancer risks are considered in absence of highly sensitive and specific screening methods as in ovarian cancer; or despite screening, most detected cancers require toxic or morbid cancer therapy, e.g., stage 1 TNBC, colorectal or medullary thyroid cancers as in BRCA1, APC and RET gene mutation carriers. Bilateral or contralateral nipple and skin-sparing risk-reducing mastectomy (RRM) with reconstruction can reduce breast cancer risk to <1% and reduce breast cancer mortality but is associated with significant complications and its impact on overall survival is yet to be demonstrated [58]. These aspects should be discussed in detail for an informed decision process. Bilateral risk-reducing salpingo-oophorectomy is strongly recommended after the age of 35 years if child bearing is complete with 1–2% residual risk of primary peritoneal cancer. In APC carriers, when endoscopic management is not feasible for the extent and nature of polyps, prophylactic total procto-colectomy with ileal pouch anastomosis or more extensive resection with colostomy is considered [59]. The American thyroid association recommends ages for RET genetic testing and prophylactic thyroidectomy as per risk



	*CANCER SCREENING OR SURVEILLANCE RECOMMENDATIONS				**CANCER PREVENTION OPTIONS	
	CLINICAL	LAB TESTS	RADIOLOGICAL	ENDOSCOPIC	CHEMO-PREVENTION	PREVENTIVE SURGERY
BREAST	+	-	+++ (MRI, MMG)	-	++ (BRCA2)	+++
OVARY	-	+ (CA-125)	+	-	+	++++
PROSTATE	-	++ (PSA)	+	-	-	-
BOWEL	-	++ (CEA, FOB)	-	++++	++ (MMR)	++++ (APC)
STOMACH	-	+ (FOB)	-	+++	-	+++ (CDH1)
UTERUS	-	-	++	++	-	+++ (MMR)
KIDNEY / UR	-	+ (UC)	++	-	-	-
ADRENAL	-	+++ (PFM, UM)	++	-	-	-
THYROID	+	+++ (Calcitonin)	++	-	-	++++ (RET)
CNS	++ (TP53, NF)	-	++ (MRI)	-	-	-
EYE	+++ (RB)	-	+++ (MRI, USG)	-	-	-
HAEMAT	+	+ (CBC, Smear)	+	-	-	-
BONE / STS	++ (NF1, TP53)	-	+++ (MRI)	-	-	-
SKIN	+++ (XP, MSH2)	-	-	-	-	-

Fig. 3 Recommendations for surveillance, chemoprevention or preventive surgery for individuals at high inherited risk of developing specific cancers. *Strength of evidence or the sensitivity of cancer screening methods from nil (−); minimal or doubtful (+); moderate (++); strong (+++) and very strong (++++). ** Strength of evidence or the magnitude of risk reduction with various prevention methods from nil (−); minimal or doubtful (+); moderate (++); strong (+++) and very strong (++++). For survival benefit, acceptability and toxicity, see text. *FOB* fecal occult blood, *PFM* plasma-free metanephrine, *UM* urinary metanephrine

level of the mutation to minimize the risk of metastatic incurable MTC [60]. Prophylactic thyroidectomy is recommended within first year of life in MEN2B codon 918 or 883 mutation carriers and in the first 5 years of life for MEN2A-associated codon 634, 620, 618 or 612 mutation and only screening or delayed thyroidectomy for other less penetrant mutations. Any risk-reducing surgery should be performed after extensive counseling regarding the pros and cons and available option. Long-term follow-up to identify and manage quality or life and survivorship issues should be adequately addressed.

9 Conclusion

The significant burden of hereditary cancer often goes unrecognized, and these families are underserved. Using a conservative estimate of 3% of all cancers being hereditary, India would have ~50,000 hereditary cancer cases annually who will require comprehensive clinical and laboratory genetic services including specialized counseling for cancer prevention and appropriate treatment. There is a need to develop culture sensitive counseling methods and generate level 1 evidence for clinical benefit for the currently recommended screening and preventive measures and develop more effective and acceptable methods. The rapidly increasing indications of genetic testing have led toward the move for mainstreaming of genetic testing, for which the practicing oncologists should acquire essential knowledge and skill.

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Library and Information

Medha Joshi

Abbreviations

EMR	Electronic medical record
ICT	Information communication technology
MeSH	Medical Subject Heading list
PICO	Population, intervention, comparison and outcome
QOL	Quality of life

1 Introduction

Medicine is an information intensive field. Patient care, research and education are three important aspects of medical domain and exist together. No education is possible without clinical work, and medicine cannot progress and medical knowledge cannot expand without the rigors of research. These aspects are inextricably intertwined and are highly information dependent. The experts are involved in all three activities—clinical, research and academics, of which the latter two result in writing, publishing or presenting at academic gatherings and may drive policy-making decisions. Clinicians need to stay updated in their field to be able to provide the best advice and healthcare to patients. Heath care is driven by two major forces—updated information and continually changing technology. In oncology, the challenges of healthcare and research are multifold. Management of cancer has holistic approach. A team with varied expertise, including nutritionists, and medical social worker have joint approach towards medical care for the patient, hence the same information has various applications and usage.

The decade of 2000, experienced huge proliferation of information communication technology (ICT) and Internet. Wide proliferation of web resources brought a sea change in the collection and dissemination of information. The technology in general and specifically Internet has not only expanded the base of information resources but has significantly changed the way information is searched and accessed. With immense technological advancements and its appropriate applications like—database integrations, mobile apps, several types of search and discovery tools, increased the ease of accessibility to information, causing a significant shift in the way doctors' source clinical information [1]. The pressing need for recent information and evidence-based practice ensured that the Internet became an essential tool as it contains the most up-to-date information in vast quantities [2]. With continuous expansion in medical knowledge, it is challenging for doctors to keep abreast of the latest evidence and therapeutic recommendations. This challenge is particularly high for residents, since as junior doctors, they do not have the experience and knowledge base of their seniors [3]. Electronic or online resources, due to their ease of availability and accessibility on various devices, are most preferred by clinicians [1–4]. This digital mobility of information through various channels makes it incredibly easy to access information from anywhere and on variety of devices. Information and technology literacy are, therefore, necessary to determine what is important in the context of the need.

2 Growth of Literature

It was predicted that by 2020 more than 40 zettabytes (or 40 trillion gigabytes) of digital data would be generated and termed as 'data deluge' by data scientists. It is expected that more than 2.5 million scholarly articles will be added every year to already existing bank of about 50 million scholarly journal articles [5]. The ever-growing volume of literature has made it impossible to effectively search and keep pace with reading. The growth of electronic media, networked information and proliferation of web not only changed the way in which information is queried and sought but also democratized the end users. Medical literature is also growing by leaps and bounds. PubMed indexes more than 35 mil-

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lion articles from about 5000 biomedical journals [6]. Oncology is a rapidly developing field with a growing number of publications every year. A quick PubMed search for Mesh Term 'Neoplasm' without assigning any limits resulted in 3,024,268 citations. Several informal channels also generate information like hospital generated data both in printed and multimedia formats, viz., electronic medical record (EMR), audio visual formats (teaching pathology files, surgical videos), raw data, blogs, personal communications (written and verbal), unpublished reports like research reports and several other sources, which are not indexed and difficult to locate. Answers to information needs may also be embedded in these sources and are often referred.

3 Information Needs

Information needs of clinicians can be categorized as related to clinical or service and academic and research. These are of varied types and complicated and are made at various settings—private practice, critical care, etc. and which may or may not be expressed. These information needs of clinicians are rarely simple, time bound and are associated with day-to-day work, related to various aspects of patient care like challenging diagnosis, treatment decisions or unexpected complications, lack of self-sufficiency and or gaps in the current knowledge, or are sought for future use. Inability to answer patient specific questions with general resource, difficulty and locating appropriate information often led to doubts, if the information really existed as ready to use material. Some needs are immediate while some may be long term with constant need of periodic updates on a particular topic. Decision making, seeking new ideas, opinions, solution to a particular problem, data validation, academic need, answers to queries raised by colleagues, peers or patients, research related or long-term unanswered issues are few of the factors that raise information needs and queries. Clinicians need rapid access to concise answers that are easy to find and help in decisions and actions [7]. The queries may be self -initiated or posed by colleagues or patients, although answers to all queries may not be pursued.

Information is mainly sought for gaining current knowledge, updates, solving problems, validating, clarifying doubts and similar matters related to domain activities. Clinicians not only require comprehensive but also look for critical appraisal of the medical literature and with many points of view. Jerome demonstrated that many questions require representation of more than one viewpoint for holistic view and complete answers [8]. Information needs in oncology are complex and dynamic, due to multidisciplinary approach to cancer care. An evidence-based work culture among the clinicians has given rise to need and search of information with different perspective.

A study observed that onco-physicians reported to have at least one question for every four or five patients. While in outpatient primary care setting, it was observed that on an average, about two clinical questions were generated for every three patients, and higher numbers reported in the inpatient teaching setting [9]. It is observed that answers to all questions are not searched.

In a user session of the biennial KRM seminar, the clinicians narrated their varied experience in obtaining necessary information while preparing their articles, reports and theses. Some of the challenges identified were: inadequate hands on training to handle the digital resources, unavailability of patient records online and within library, search ability and accessibility to institutional old publications, very little data on Indian cases, non-availability of full text of articles and few technological challenges like weak connectivity to internet [10].

Information need is often clubbed with published literature and real time clinical data from patient health record (EMR) and factual information to serve both clinical and academic/research information needs. Information needs for academic and research activities are different from that of clinical queries. In a clinical setting, the need is patient oriented, situational and personalized toward patient, hence the timely need of precise information. The need for precise and ready to use quality materials is required in evidence-based approach to support clinical decisions.

4 Example of Clinical Query

Topic: use of Botox in patient with total laryngectomy for voice rehabilitation

Context: Patient care—quality of life (QOL)

Background: Patients who undergo total laryngectomy loose voice completely. Patients' speech is then assisted by machine, which is not very comfortable, has poor clarity and affects the quality of life. A research outcome for patient who undergo this treatment and their voice quality was observed and conduct similar study in-house.

Information needs: (1) Background information, clinical trials publication, research publications in journals; (2) Information in Indian context. So, what was required, is a literature search for published information on above query and its outcome with emphasis in Indian context. While discussing with clinician (a typical reference interview), it was observed that comparative information was also required.

Books were referred to collect background information; journal articles were searched in PubMed, and IndMed and MedInd. The last two resources are databases for articles published in Indian journals. The purpose of **IndMED** is to index selected peer reviewed Indian medical journals, while MedInd is one-point resource of Indian biomedical literature covering full text of **IndMED** journals.

Research and academic activities require high volume of information. Information is sought on a research question, hypothesis formulation, what is reported, active researchers and also factual information, which depends upon the type of research being planned or conducted. A typical clinical trial will need information specific to the problem, while an academic research in part fulfillment of degree may not need focused information, but as the research progresses, the need may shift to pointed questions. Academic needs may be related to teaching, conference presentations, writing books, research papers, reviewing activities or preparing for examination.

5 Example for Research Need Query

Topic: A study on pain management and perception of pain by patients

Context: Writing a study report

A study was conducted on pain management and patients' perception of pain. The objectives of the study were perception of pain by patients because of (a) side effects and (b) actually due to disease. The study sought to examine cultural and ethnic influences on perception of pain, easy addiction to analgesics and whether patients perceived complaints to primary physicians as a waste of consultation time or a distraction from the main focus on the disease. The study was questionnaire based.

Information need: what is reported and comparative information and information in Indian context.

Searches: PubMed, Nursing database, MedInd and IndMed were searched, but did not yield good results. Search was further supplemented using Google scholar. Few references in non-medical and nursing journals were found. The full text of few related articles was obtained through cited references.

6 Patient Education

Oncologists routinely educate patients and address individualized information needs on variety of topics during consultations, to enable patient's informed participation in decisions regarding disease management [8]. The information leaflets distributed to patients are informative about their disease, but may not address practical questions like "what if/incase of" situations [11–13]. Health awareness amongst consumers and patients is rising in India, and patients' approach to libraries for reading materials has also risen. Several resources, websites and information embedded within commercial resources, are available that can help in creating 'made to request' information material. Collaboration between clinician and librarians can support such needs. 'Medline Plus' of NLM addresses consumers and patients' health information needs. Awareness of availability of ready resources and its consultation is essential amongst clinicians. The diagnosis and treatment of cancer can present a major challenge to patients. Fears of longevity, tests and treatments, side effects of treatment, difficulties in adjusting to physical changes like body appearance and functioning, social disruption, financial concerns and religious beliefs are some concerns that have to be addressed through education. Although it is known fact that patients use Internet for information, they prefer to receive personalized written information from their health care provider, and medical humanities plays an important role in cancer management [11–13].

7 Preferences of Sources and Searching

A routine in-house survey observed that oncologists preferred e-journals. A survey of oncologists in Mumbai city also indicated the same and observed that preferences for e-journals [14] were based on authenticity and currency of information with easy and quick accessibility. Searching online journals for research articles was the first choice rather than systematically searching e-databases. Often there is a need to refer to various resources at a time - subscribed resources, web-based free resources and in-house generated resources like EMRs, cancer registries and scientific reports to answer complicated queries. The requirement to refer individually or combination of these resources at a time, depends upon the purpose for which the information is sought. Linkages to these varied sources with single point search and access are the need of the hour, and hence discovery tools or web scale information search engines are in demand. Common search interfaces, common search windows or federated searches are therefore often found on library webpages.

The electronic journals were highly impacting resource, especially in medicine. However, a shift on preference of sources has been observed during past few years. Oncologists are more confident searching scientific databases [15]. The information needs of oncologists significantly differ from the other medical experts and have different ways to access specific information [16]. The information support for whatever purpose is proportional to the user's awareness of resources, searching skills and library services.

Clinicians and specially residents are unaware of search techniques, digital resources and do not observe libraries as service providers and gateways to information. Time constraint, uncertainty, peer support and unable to locate appropriate source are some of the reasons for not seeking answers to all questions [15, 17]. Background knowledge of search tools and strategies, usage of resources and comfort level with technology decide on how clinicians identify and respond to information gaps [17].

Literature search is a daunting task and the challenge of searching, locating and quick delivery of document is immeasurable. Many physicians have concerns about finding of the right resources and identifying the authoritative resource on the web [15]. They fear searches would result in too many or too few citations, or irrelevant articles, causing loss of time.

An effective searching depends upon three components, viz., appropriate database/resource selection, domain knowledge and search technique and skills. Information search is an essential component of the research process. A review of the literature on a specific topic or clinical question is crucial for academic study and professional development, to create and publish secondary analysis on a specific topic. Asking the right answerable question and appropriate resource selection is key to searching appropriate and relevant information. A broad question will give too many results, and manual filtering would be tedious. It is therefore necessary to first understand the nature and purpose of the information query. The purpose directs the selection of the resources. Information queries can be categorized as back ground questions and foreground questions. Answers to background questions are usually found in medical text books, handbooks or resources like point of care tools—first consult, or descriptive or narrative reviews which take an overview of the topic over a period of 5–10 years. Answers to foreground questions are usually found in secondary information resources which provide availability about and accessibility to information, that is an abstracting and indexing resource or databases like Medline, PubMed, EMBase, CINAHL and Cochrane (systematic reviews), ACP Journal club and other synthesized resources. It is always better to begin a search using a database when we are looking for foreground information, as it saves time and searching across several journals is easier.

Information is flowing in from all quarters, and in all forms and formats. Information overload is overwhelming and handling it is difficult if searches are not planned properly. Effective searching has always been a challenge to clinicians' especially junior doctors, as they are not exposed to search techniques and search skills. Ely identified about 59 obstacles encountered by clinicians, viz. [18] difficulty in modifying original question, open questions, difficulty in selecting an optimal search strategy; failure in topic coverage by seemingly appropriate resource; uncertainty about how to know when all the relevant evidence has been found and stop the search and inadequate synthesis of multiple bits of evidence into a clinically useful statement.

It is observed that information resources supported clinicians' needs related to patient care—diagnosis, choice of drug, etc. and enabled better informed clinical decisions and impacted patient care [19]. Strategic planning and a little homework prior to searching help in addressing these difficulties and conducting an effective search. Understanding the requirement and selecting appropriate resource sets the stage for a good search. A methodical approach in formulating a query that the system understands will ensure good and relevant results. A strategic planning will consist of answers to the following questions, as preparation for search.

- What is that I am looking for (i.e., finding the focus of the question)?
- What are the key concepts (ideas) embedded in the question?
- What do I know about these concepts (i.e., understanding of these concepts)?
- What are the alternative and variant terms that describe each of these concepts?
- Where do I start searching?

It is not enough to know the resource, but it is more essential to know the appropriate one, and how to use it effectively. There are several resources and each one is focused - domain and information format (see Table 1 for key resources for oncology and Table 2 for guidelines). Searching is database structure dependant. Pre-requisites required for effective searching are domain knowledge,

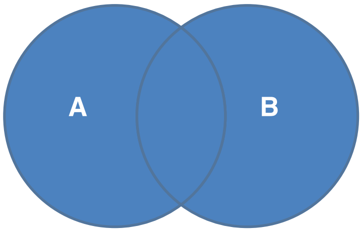
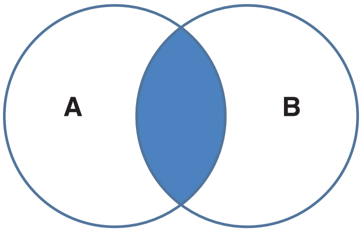
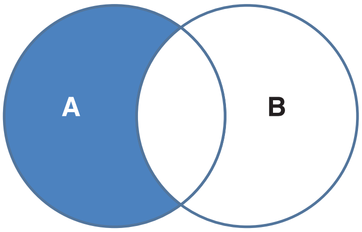
Table 1 Useful resources

Purpose/Utility	Resource	Operators used	Proximity operators used
Citation searching—Biomedical and medical	PubMed, Medline	AND, OR, NOT	None
	OVID—Medline, OVID—Psychinfo	AND, OR, NOT	NEAR, FREQ
	EMBase	AND, OR, NOT,	NEAR/n finds words near within no. of word on both sides NEXT/n—within 'n' words of each other
	Web of Science	AND, OR, NOT	NEAR—Nx X = upto 15 word
	SCOPUS	AND, OR AND NOT	WITHIN—W/n Preceded by—Pre/n $N = 0–225$
	MedInd	–	–
	IndMed	AND, OR, NOT	–
Citation searching—Nursing	CINAHL	AND, OR, NOT	NEAR—N/x WITHIN—W/x
EBM resources	Cochrane systematic reviews	AND, OR, NOT	NEAR within = 6 words of each other NEAR/X, X = no. of words within each other NEXT—words next to each other like ADJ
	BMJ best practice		
	DynaMed	AND, OR NOT	
	UpToDate	–	–

Table 2 Practice guidelines and other resources

Resource	URL	Publisher	Remarks
Guidelines	Evidence-based recommendations		
ASCO practice guidelines	https://www.asco.org/practice-guidelines	American Society for Clinical Oncology, USA	Educational resources, provides clinical practice and quality guidelines. Also list under development guidelines
ESMO	http://www.esmo.org/Guidelines	European society for medical Oncology, Switzerland	Guidelines by cancer sites
NCCN	https://www.nccn.org/professionals/physician_gls/default.aspx	National Comprehensive Cancer Network, USA	Contribution from 27 cancer centres on various cancer sites
NICE	https://www.nice.org.uk/guidance	National Institute of Health and Care Excellence, UK	Covers clinical, social, public health, quality guidelines and others, sorted by condition, disease, lifestyle etc.
EBM from TMC	https://tmc.gov.in/tmh/index.php/education-and-research/publications/evidence-based-management-guidelines-ebm	Tata Memorial Centre, Mumbai	Annual publication on different cancer sites—management
Clinical Trials	Registry of clinical trials conducted all over, generally provide information on ongoing accrual, trial sites, etc.		
International	https://clinicaltrials.gov/	From NIH, National Library of Medicine, USA	–
	https://www.globaldata.com/healthcare/research-areas/pharmaceutical/clinical-trials/	Globaldata, London, UK	Covers trials across more than 40 countries
	http://www.eortc.org/clinical-trials/	**EORTC**—European Organisation for Research and Treatment of Cancer. **Brussels**	–
	http://www.who.int/ictrp/en/	International Clinical Trials Registry Platform (ICTRP), by World Health Organization	• Search by health topics, countries and regions
Clinical trial registry India	https://tmc.gov.in/tmh/index.php/education-and-research/publications/evidence-based-management-guidelines-ebm	National Institute of Medical Statistics, New Delhi, India	–
Factual information	Cancer fact sheets by cancer site—related to incidence and prevalence		
Global Cancer Observatory (Globocan)	https://gco.iarc.fr/	International Agency on Research on Cancer—World Health Organization	Worldwide fact sheet for cancer incidence, mortality, prevalence, age, gender and cancer site
National Cancer Registry Programme	http://www.ncrpindia.org/	National Centre for Diseases Informatics and Research, New Delhi, India	–
ICMR—National Cancer Registry Programme	http://www.icmr.nic.in/ncrp/cancer_reg.htm	ICMR, New Delhi, India	Nationwide, Consolidated Population based and hospital based registries. Updated only up to 2004
Cancer Atlas, India	http://www.canceratlasindia.org	National Centre for Diseases Informatics and Research, New Delhi, India	–
Hospital based cancer Registry	www.hbcrindia.org	National Centre for Diseases Informatics and Research, New Delhi, India	–
Formulary	**Drug information**		
British National Formulary	www.medicinecomplete.com	Pharmaceutical press	Drug information
National Formulary	http://www.cdsco.nic.in/writereaddata/NFI_2011%20(1).pdf	CDSCO, India	Drug information

Table 3 Connectors/operators and their use

OR	**AND**	**NOT**
 A OR B Will retrieve citations with terms ‘A,’ ‘B’ and ‘AB’	 A AND B AB = cancer **AND** women	 A NOT B Citations with only the term ‘A” retrieve citations—**‘A,’ neither ‘AB’ nor ‘B’**
• Hamburger OR eggs OR Both terms in citations • Nutrition OR diet OR Both terms in citations	• Toxicity of Lead—Lead AND Toxicity • Calcium in women—Calcium AND Women • Nutrition for Infants—Nutrition AND Infant	• Dementia **NOT** Alzheimer’s • Diet **NOT** Vegetarian
NEAR	**WITH**	**ADJ**
Ex.—Research NEAR2 Dyslexia Tells the data base to search the two terms within in vicinity of 2 words in between	**Ex**.—Effect WITH Effluent The two terms have one word in between and in the same sentence	**Ex**.—Curcuma ADJ Longa The two terms have to be next to each other without any other term in between and the order is as typed

appropriate selection of database/resources and knowledge about the search interface.

Once keywords, or key-terms or descriptors are identified, small search statements are made on the databases for each concept and finally all search statements are combined using Boolean logic and presented to the system, which shows final results. These statements or keywords are combined using ‘connectors’ called Boolean operators (logic)—AND, OR NOT in most databases (PubMed, MEDLINE, CINHAL, etc.). The AND, OR NOT have specific role to play in the search statement. They either broaden the search results, narrow and limit the search or eliminate a particular aspect in the search query. Many databases like Biological Abstracts may also include other types called proximity operators, viz., NEAR, WITH and ADJ. These are usually used to indicate the appearance of related keyterms/words in literature and help on focusing on the terms (Table 3).

Building search strategy is like building a wall, where terms are bricks and ‘connectors’ are adhesives. When there are complex queries, break query into concepts, search key term/descriptors/keywords for each concept independently and then combine all statements using operators for final results.

8 Summary

- Boolean operators are used in PubMed, CINHAL, MedLine, EMBase and Cochrane
- AND is used to connect concepts when both or all must be present
- OR is used to group synonymous terms when at least one must be present
- NOT is used to eliminate articles containing the specified term.

PubMed is the key database for all medical and biomedical literature. This is the first database to go to incase of information need. Along with Boolean operators, PubMed interface where all databases fields are searchable and can be combined using Boolean operators and the search results can be further limited by age, gender, type of studies, format of document like review, case report, years of study, etc. within the databases combine searches to refine the search results. Apart from being a strong database, its strong indexing system and use of Medical Subject Heading list (MeSH) to index, tag and classify the citations within Medline database helps in focusing searches. Mesh terms can be used to select citations based on their focus of discussion. Since PubMed/Medline are the most appropriate database for searching medical literature/citation, the following examples are in context with searching PubMed, in order to provide an idea on the searching technique, skill and use of database features. Although the description and examples are from PubMed, most databases in medicine use MeSH and follow the same search heuristics perhaps with slight variation. These simple heuristics of searching can help in formulating appropriate search statements and effective results.

9 Example of Search Strategy (PUBMED) Using Boolean Operators

Topic: Publication on use of TRAM flaps in plastic reconstruction for breast cancer patients

Concepts: Flaps, Breast cancer patients, Reconstructive surgery

Search strategy

#1 TRAM flaps [ti/ab]

#2 Reconstructive surgical procedures [MeSH]

#3 breast cancer [ti/ab]

Combine above statements—#1 AND #2 retrieves 143 citations

Combining #1 AND #2 AND #3, retrieved 40 citations on PubMed

In the above search, the statement indicated to the database to search ‘TRAM flaps’ in title and abstract field, so that focus is maintained and the MeSH terms were used for “procedures” to ensure the discussions were about the procedures in the articles. It is essential to note that all boolean operators and proximity operators are always presented in Capitals and must not be used as English language conjugations.

10 Evidence based Medicine

Searching for evidence-based medicine needs tools to formulate query and are also used for forming search strategy, viz., PICO and SPIDER, of which PICO is very popular.

PICO stands for **P**opulation, **I**ntervention, **C**omparison and **O**utcome.

Stages in search:

- Identify key concepts using PICO.
- Determine alternative terms for each concept.
- Define search dates, study groups, etc.
- Formulate a final search statement, using Boolean logic.

Other tools, like PICOT (where T is the period of data collection) and SPIDER (Sample, Phenomenon of interest, Design, Evaluation, Research type), are usually recommended for searching qualitative and mixed research methods. However, PICO is most common and highly recommended tool. In effect, these tools help us to break our need in to different components and helps us to focus on the actual information need. Once the focus of question is identified, the next step is to identify keywords, and alternative words for each concept, and lastly help us to identify appropriate resource.

11 EBM Example

Results of phase III clinical studies (interventional/of drugs) conducted in patients of platinum resistant ovarian cancer (results published in the last 5 years) (Figs. 1 and 2).

P = Patients with resistant ovarian cancer

I = drugs

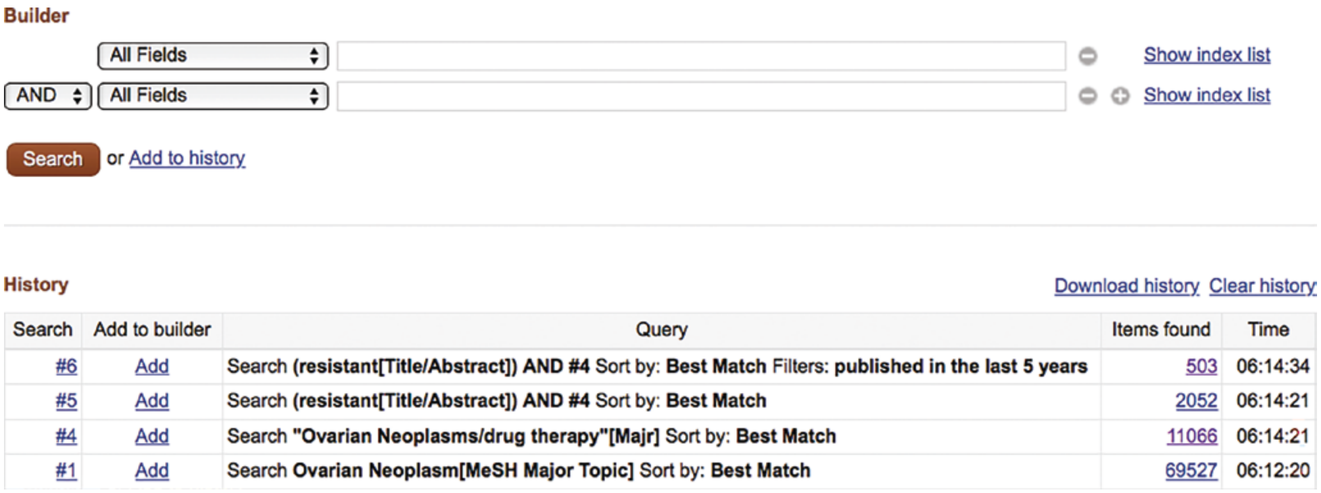
C = platinum resistant

O = effectiveness

(Ovarian neoplasms [MeSH]/Drug [Majr]) AND (resistant [Title/abstract])

Resource used—PubMed., Cochrane, PubMed Clinical Queries

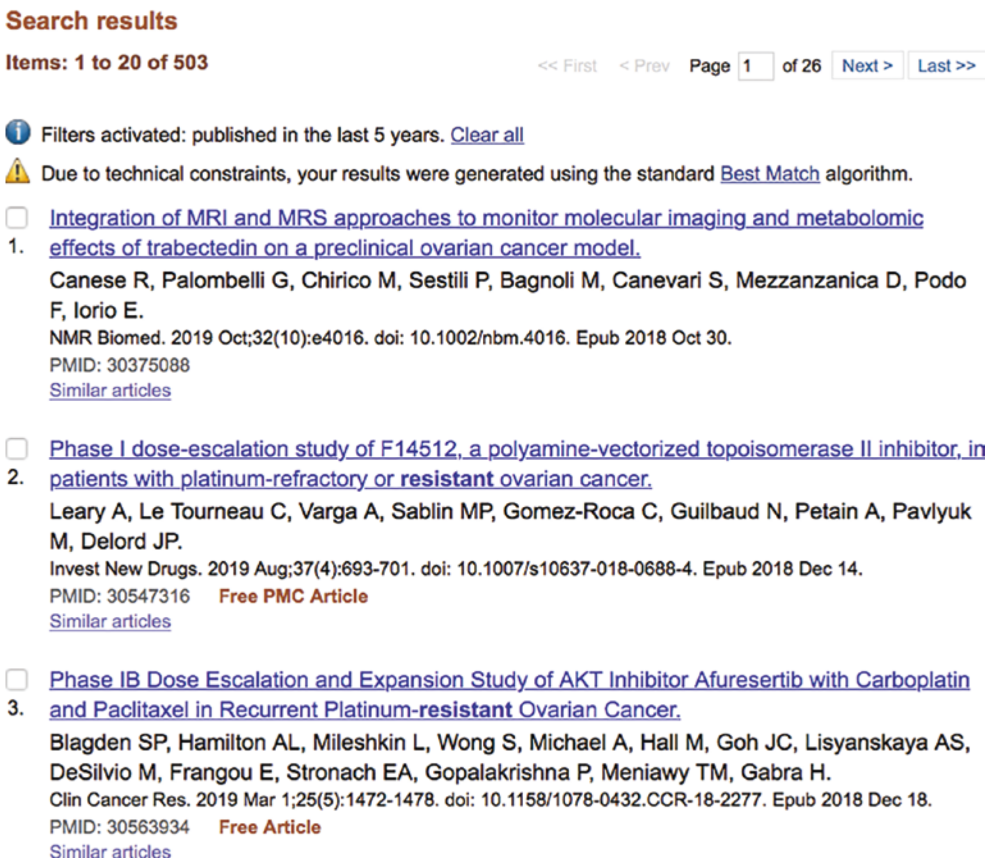
Cochrane library consists of four databases, of which systematic review database is a collection full text of systematic reviews of randomized clinical trials, i.e. analysis of the results using statistical synthesis of data (meta-analysis) to establish evidence.



Search	Add to builder	Query	Items found	Time
#6	Add	Search **(resistant[Title/Abstract]) AND #4** Sort by: **Best Match** Filters: **published in the last 5 years**	503	06:14:34
#5	Add	Search **(resistant[Title/Abstract]) AND #4** Sort by: **Best Match**	2052	06:14:21
#4	Add	Search **"Ovarian Neoplasms/drug therapy"[Majr]** Sort by: **Best Match**	11066	06:14:21
#1	Add	Search **Ovarian Neoplasm[MeSH Major Topic]** Sort by: **Best Match**	69527	06:12:20

Fig. 1 Screenshot of Search builder _ search strategy using PubMed 'Advanced' search feature

Fig. 2 Search results—PUBMED



Filters activated: published in the last 5 years. Clear all

Due to technical constraints, your results were generated using the standard Best Match algorithm.

☐ 1. Integration of MRI and MRS approaches to monitor molecular imaging and metabolomic effects of trabectedin on a preclinical ovarian cancer model.
Canese R, Palombelli G, Chirico M, Sestili P, Bagnoli M, Canevari S, Mezzanzanica D, Podo F, Iorio E.
NMR Biomed. 2019 Oct;32(10):e4016. doi: 10.1002/nbm.4016. Epub 2018 Oct 30.
PMID: 30375088
Similar articles

☐ 2. Phase I dose-escalation study of F14512, a polyamine-vectorized topoisomerase II inhibitor, in patients with platinum-refractory or **resistant** ovarian cancer.
Leary A, Le Tourneau C, Varga A, Sablin MP, Gomez-Roca C, Guilbaud N, Petain A, Pavlyuk M, Delord JP.
Invest New Drugs. 2019 Aug;37(4):693-701. doi: 10.1007/s10637-018-0688-4. Epub 2018 Dec 14.
PMID: 30547316 Free PMC Article
Similar articles

☐ 3. Phase IB Dose Escalation and Expansion Study of AKT Inhibitor Afuresertib with Carboplatin and Paclitaxel in Recurrent Platinum-**resistant** Ovarian Cancer.
Blagden SP, Hamilton AL, Mileshkin L, Wong S, Michael A, Hall M, Goh JC, Lisyanskaya AS, DeSilvio M, Frangou E, Stronach EA, Gopalakrishna P, Meniawy TM, Gabra H.
Clin Cancer Res. 2019 Mar 1;25(5):1472-1478. doi: 10.1158/1078-0432.CCR-18-2277. Epub 2018 Dec 18.
PMID: 30563934 Free Article
Similar articles

12 Staying Updated

The most important need and challenge for clinicians is staying updated in their domains. It is humanly impossible for any individual to read the voluminous literature and assimilate the knowledge. The information is generated and made available on several formats and search platforms. Several trials conducted across the world, add to the knowledge base of about potentially effective treatment. To keep a hawk's eye on the new developments no matter how niche the domain is, is humanly impossible. Almost all resources provide 'alerts' on chosen topics, or 'table of contents' (TOC) as e-mail services. Several web-based information systems are also available, and many individual institutions have invested in federated search or discovery tools and artificial intelligence systems to seek answers, where user profiles can be generated to stay updated.

PubMed search statements can be saved and set to receiving alerts as email every time new citation is added to PubMed through 'My NCBI' account. Subscribing to RSS feed is another way to receive updates in mailbox.

Information is gathered and stored for use, reuse, recycle and regeneration. Gathering of useful citations is like creating your own library for present and future use. Managing collections of citations and articles is therefore equally important. Use of citation management tool from the beginning is recommended. There many free and subscribed citation management tools. These are embedded in Word processing software and operate on all browsers, which help in auto-downloading of the citations and easy to insert citations in manuscript in the preferred format and style effortlessly.

Libraries in digital scenario are gateway to information and strive to make e-resources available and accessible at one search. The libraries not only update collection but also adopt new supportive technologies and are trained in search and retrieval. Medical librarians can substantially support information needs related to clinical questions or academic queries. They have diverse roles apart from management of electronic resources. They are continuously engaged in user instruction and support clinical research needs and provide information search and retrieval services. When deprived of time, or difficulty in search or locating resources, it is always good to consult library professionals, who can serve as intermediaries and add value not only in identifying appropriate resources but also conduct effective searches. Being digitally literate is necessary and can be attained by reaching out to librarians for an information literacy tutorial and asking for search support. It is a well-established fact that when searches are conducted jointly with medical librarians, the results are more appropriate.

In spite of all preparation, it may happen that search results are not satisfactory. It must be remembered that information search is a reiterative process, and if results are unsatisfactory, a relook at query, concepts, keywords, database selection and statements is necessary.

13 Summary

- Plan your search well.
- Identify concepts or use PICO formula.
- Identify key terms/keywords/descriptors for each concept.
- Choose appropriate database.
- Make search strategies for each concept and run the searches.
- Combine all searches.
- Keep record of search statements, results retrieved.
- Browse, select relevant citations and download/save to citation managers.
- Difficult to locate—consult your librarians.

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Oncology Training and Education in India

Siddhartha Laskar, Anant Ramaswamy, Garvit Chitkara, and Shripad D. Banavali

1 Overview

The availability of trained and skilled manpower besides an appropriate infrastructure are important pre-requisites to the delivery of optimal cancer care. Specialty education in cancer diagnosis and treatment has been a mandate of the founding fathers of Tata Memorial Centre (TMC) since the time of its inception in 1941. Sir Nowroji Saklatwala and Mr. JRD Tata encouraged and inculcated the concept of comprehensive cancer care along with education and research. Sir Roger Lumley, the then Governor of Bombay appreciating the vision of the Dorabji Tata Trust, said in his inaugural address '… *You are attacking it on the three fronts of Treatment, Education and Research—all three of them essential and interdependent—I must express my admiration for the completeness of your plan'*.

Cancer care and options for treatment across the stages of cancer have exponentially increased with a surfeit of diagnostic tools and management strategies being available and applicable. After having started in mid-twentieth century, the cancer training programs in India have matured into more focused and specialized courses and train a sizeable number of doctors trained in various facets of cancer treatment. These doctors not only contribute to the cancer care but also take active part in research and education. The total number of cancer cases in the India have steadily increased [1]. Concurrent with the exponential increase in patient numbers, there has also been significant increase in complexities of treatment and an explosion in scientific information that one needs to understand and assimilate. Despite the increase in training programs to address the growing needs of qualified personnel, there is still a big gap that needs to be filled both in quantitative and qualitative terms.

The National Eligibility Cum Entrance Test (NEET) 2020 and the National Medical Commission (NMC) database mentions 18 institutions offering 79 placements for DM Medical Oncology programs, 23 institutions offering 98 placements for MCh in Surgical Oncology and 87 institutions offering 594 placements for MD in Radiation Oncology across the country. Additionally, few deemed institutions like the All India Institute of Medical Sciences (AIIMS), New Delhi and Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Puducherry also have training programs in various specialities of oncology. It is also essential to note that besides the MD/DM/MCh training programs, training in oncology is also offered via the Diplomate of National Board (DNB), under the aegis of the National Board of Examinations (NBE), New Delhi, an autonomous academic body under the Ministry of Health and Family Welfare.

2 Education and Training at Tata Memorial Centre (TMC), Mumbai

Cancer education and training have always been areas of high priority at TMC. The division of academics at TMC was established in 1982 and is affiliated with the Homi Bhabha National Institute (HBNI), a deemed university of the Department of Atomic Energy (DAE), Govt. of India. The courses offered in TMC can broadly be classified into the streams of Health Sciences at Tata Memorial Hospital (TMH), Parel and Life Sciences at the Advanced Centre for

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Treatment, Research and Education in Cancer (ACTREC), Kharghar. The institute conducts a wide range of courses recognized by the Medical Council of India (MCI)/National Medical Commission (NMC). The courses include MD, DM/MCh programmes in oncology (e.g., Radiation Oncology, Medical Oncology, and Surgical Oncology) and other related subjects (e.g., Anesthesiology, Radiology, Nuclear Medicine, Microbiology, Immuno-Hematology & Blood Transfusion Medicine, Pathology, Palliative Medicine). Superspecialty courses like DM in Pediatric Oncology, Critical Care, Oncopathology, Interventional Radiology and MCh in Head and Neck Surgery and Gynecological Oncology at TMC have been introduced for the first time in the country.

Besides training programs for the broad and superspeciality subjects, TMC offers post graduate training in subjects like Advanced Diploma in Radiation Therapy (ADRTT), Imaging Technology (ADMIT), Nuclear Imaging (PGDFIT), Nursing Oncology along with Masters courses in Nursing Oncology and Clinical Research. The training program on patient navigation (KEVAT) is unique and is another first in the country. TMC also offers multiple fellowship programs under the umbrella of the HBNI in varied specialities.

The teaching programs include classroom lectures, seminars, bedside clinics, hands on practical training and informal discussions. Significant emphasis is laid on practical training and self-learning. These are considered very significant training components for technical skill development, decision-making abilities, confidence building, coordination and team work.

The Academic Research Program at ACTREC focuses at providing an in-depth insight into diverse areas of Life Sciences with emphasis on Cancer Biology in an attempt to unravel the molecular mechanisms responsible for many manifestations of cancer using in vitro cell line and animal model systems. The Centre has a very active Ph.D. program in Life Sciences under the HBNI. The research interests cover a wide range of topics including areas like mechanisms of carcinogenesis, the underlying genetic changes that could bring about this transformation, mechanisms of disease spread, reasons underlying treatment resistance, the impact of environment and lifestyle, etc. Short-term training spanning 1 to 6 months is offered to students (Bachelor's or Master's) to conduct research as a part of their curriculum under the guidance of principal investigators of the centre in specific areas of Cancer Research. Programs are available for faculty/teachers/staff or doctoral students of academic/research institutions who wish to learn specific techniques. Short observership programs are available for students or faculty of academic or research institutions who wish to observe specific techniques and training opportunities are also available for M.Sc.(I/II) students during their college summer breaks for periods of 1–2 months.

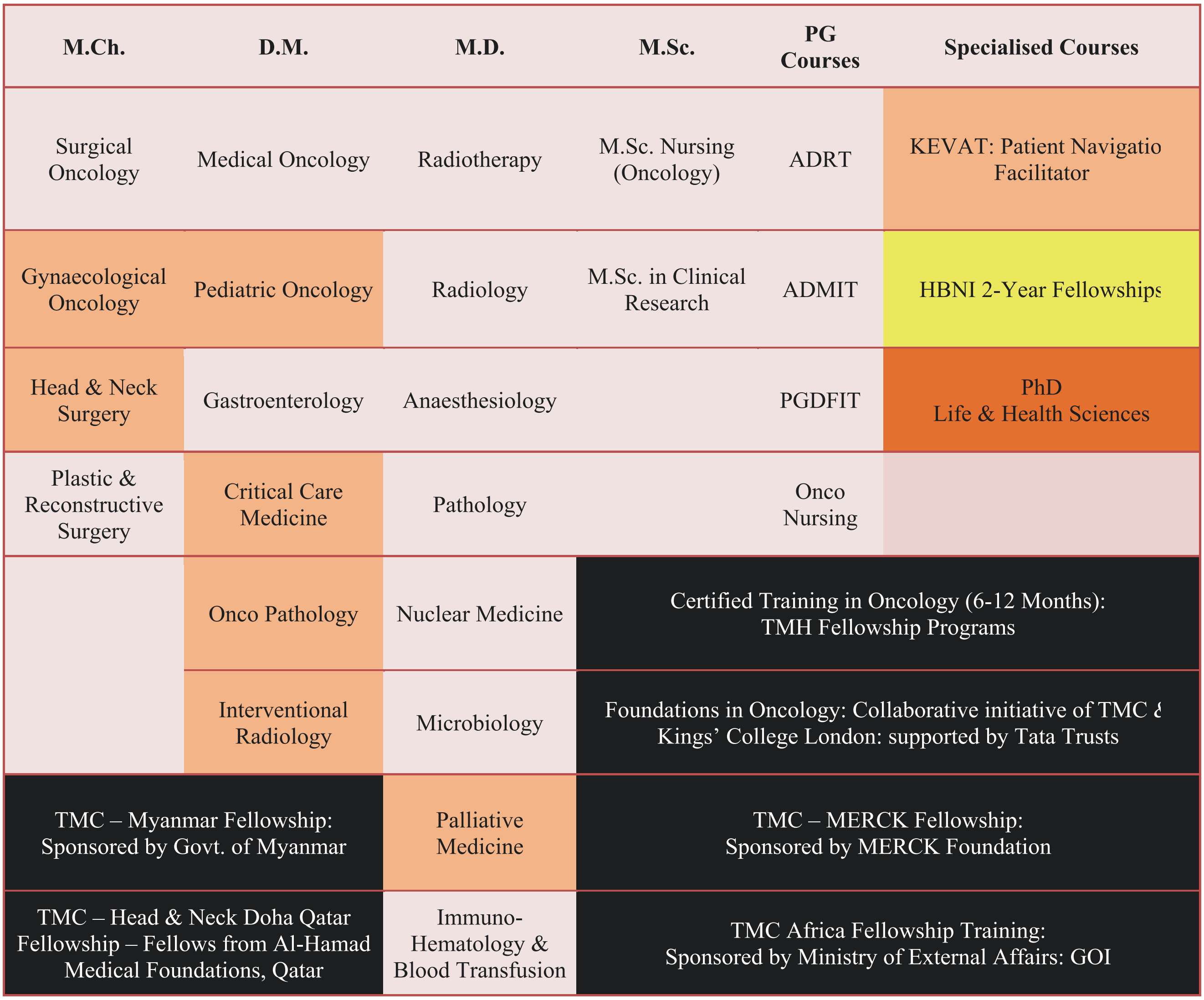
Practical hands-on trainings and workshops that are essential components of training in comprehensive cancer care are regular features of the educational programs in the institution. The ongoing courses at TMC are continuously reviewed for quality and new courses added to address the growing needs.

The Bone Marrow Transplant facility was relocated from TMH to ACTREC in November 2007. Approximately 800 allogeneic and autologous transplants have been performed in ACTREC since then. Since 2009, unrelated donor transplantations and haploidentical transplantations are being routinely performed in appropriately selected patients. There is a social scheme in place for deserving, economically backward patients who have highly curative disease but do not have the finances to undergo autologous or allogeneic transplant. ACTREC offers a 1-year fellowship in BMT for medical oncologists having completed DM and also a 1-year BMT nursing fellowship.

The Proton Beam Therapy Centre at ACTREC is the first state of the art particle therapy facility in the public sector in India. Besides catering to the treatment needs of patients from within the country and abroad, this centre is focused on research aimed at generating robust evidence for optimizing the use of proton therapy in various cancers. Training and human resource development of personnel ranging from clinical oncologists, physicists, technologists, engineers and scientists is another thrust area for this centre.

TMC also conducts training programs for sponsored candidates from State Government Medical colleges, Central Government Hospitals, Public Sector Undertaking Hospitals and Regional Cancer Centres across the country (Table 1). TMC provides training programs and courses for specialists and trainees from the region providing training in the field of oncology and related subjects to doctors and allied specialities.

Table 1 Education and training programs at Tata Memorial Centre, Mumbai



M.Ch.	D.M.	M.D.	M.Sc.	PG Courses	Specialised Courses
Surgical Oncology	Medical Oncology	Radiotherapy	M.Sc. Nursing (Oncology)	ADRT	KEVAT: Patient Navigatio Facilitator
Gynaecological Oncology	Pediatric Oncology	Radiology	M.Sc. in Clinical Research	ADMIT	HBNI 2-Year Fellowships
Head & Neck Surgery	Gastroenterology	Anaesthesiology		PGDFIT	PhD Life & Health Sciences
Plastic & Reconstructive Surgery	Critical Care Medicine	Pathology		Onco Nursing	
	Onco Pathology	Nuclear Medicine	Certified Training in Oncology (6-12 Months): TMH Fellowship Programs		
	Interventional Radiology	Microbiology	Foundations in Oncology: Collaborative initiative of TMC & Kings' College London: supported by Tata Trusts		
TMC – Myanmar Fellowship: Sponsored by Govt. of Myanmar		Palliative Medicine	TMC – MERCK Fellowship: Sponsored by MERCK Foundation		
TMC – Head & Neck Doha Qatar Fellowship – Fellows from Al-Hamad Medical Foundations, Qatar		Immuno-Hematology & Blood Transfusion	TMC Africa Fellowship Training: Sponsored by Ministry of External Affairs: GOI		

- TMC in-house programs
- Programs introduced for the first time in the country
- Ph.D. programs affiliated to HBNI
- Fellowship programs affiliated to HBNI

3 The National Cancer Grid (NCG)

The NCG is an initiative of the Tata Memorial Centre, Mumbai supported by the Department of Atomic Energy (DAE), Govt. of India and the Tata Trusts. It was created to form a union of cancer centres in the country which could provide uniform and high standards of cancer care, follow uniform evidence-based guidelines for management of patients, provide training and education in oncology and facilitating collaborative basic, translational and clinical research in cancer to fulfill the cancer healthcare needs of the entire nation.

Aims and objectives include the following:

- Evolve and implement uniform standard of cancer care across India.
- Offer the state of art services for those afflicted by cancer.
- Create human resources to tackle the rising need of cancer care.

- Gauge the magnitude trend and type of national cancer problem through registry and run appropriate epidemiological intervention studies to prevent cancer.
- Direct cancer research in clinic and laboratory to offer cost-effective solution to cancer in India.

Some of the established educational tools offered by the NCG are as follows:

- Virtual Tumour Board (VTB)
- Online Learning
- Travelling School of Pathology
- CReDO Workshop/Research Webinar

Towards the NCG efforts in quality improvement, the NCG hosts educational programs like Quality Improvement Hub (QI Hub) in collaboration with Stanford Medicine (USA), a leader in educational programs for quality improvement for clinical teams. Such programs are designed at providing the participants with conceptual understanding and experience necessary to respond to quality related problems across a complex environment such as clinical practice settings.

4 Summer School in Oncology

Tata Memorial Centre in partnership with King's College, London and supported by the Tata Trusts have initiated this course for undergraduate students pursuing MBBS and those in their early years of post-graduation after MBBS. The module titled 'Fundamentals in Oncology (FinO)' is aimed at enhancing knowledge, skills and aptitude of medical graduates regarding cancer. It provides the student a comprehensive insight into cancer management thereby enabling participants realize their aptitude and assist students in deciding about a future career in oncology. The module lasts for 10 days following which students are evaluated by experts based on written test and interviews. Usually about 150 students participate in the course from educational institutions across the country, selected by respective deans.

Upon completion of the course, the participants receive a certificate, awarded jointly by Tata Memorial Centre and King's College, London. The top five meritorious students are offered an opportunity to undertake a week of clinical observership at Tata Memorial Centre, Mumbai and 4 weeks clinical observership at Guy's and St. Thomas' Hospital, London.

5 "KEVAT" Patient Navigation Program

In order to addresses the need for a structured patient support system for cancer care that will form a bridge between patients and access to care, the Tata Memorial Centre (TMC), in collaboration with Tata Institute of Social Sciences (TISS) and with support from Tata Trusts, introduced a 1-year (full-time) Advanced Diploma in Patient Navigation (KEVAT), for the first time in India. The patient navigation program is aimed at creating a trained task force to facilitate a patient's journey right from entry to the hospital to follow-up and getting back to normalcy, while also taking care of the patient's the emotional, economic and various other needs in a holistic way.

6 Online Oncology Tutorial Series

As a part of a national programme to train doctors about early signs of cancer, the Union Health Ministry launched its first online 'Oncology Tutorial Series'. This joint initiative of the Tata Memorial Centre, Mumbai and the Government of India uses a digital platform, 'Omnicuris', for education on evidence-based practice of cancer care in the country and to make cancer education and training accessible to everyone across the country.

The course is of seven months duration and is intended for physicians, gynecologists, dentists and medical professionals who are not trained oncologists. It has different modules based on various sites and sub sites of cancer. In its 14 h of comprehensive e-learning, it offers 40 video lectures, case studies, questionnaires and webinar sessions with professional consultants of Tata memorial hospital. At completion of the course, the participants undergo an assessment and receive a certificate of completion.

7 National Knowledge Network (NKN)

National Knowledge Network (NKN) is an initiative by the Government of India aimed at establishing a strong and robust Indian network which will be capable of providing secure and reliable connectivity interconnecting all knowledge and research institutions in the country through a high bandwidth network in order to improve access to knowledge. NKN with its broad capability aims to connect all universities, research institutions, libraries, laboratories, healthcare and agricultural institutions across the country to address the need of collaboration to enrich the research efforts in the country. The network design takes into account the future requirements and new possibilities that this infrastructure may unfold, both in terms of usage and perceived benefits. It will facilitate the development of India's information infrastructure, stimulate research and create next-generation applications and services. NKN is a significant step which is designed to enable scientists, researchers and students from across the country to work together for advancing human development in critical and emerging areas.

8 Oncology Training for the Future

There is an increasing demand for precision and personalized medicine in oncology [2] and very much like no two patients, no two cancers are similar. Increased use of Genomics, Proteomics and advent of many other similar technologies have made oncology a very dynamic and constantly changing branch of medicine. With the constantly changing therapeutic options in medical, surgical and radiation oncology, it is important for training also to keep changing accordingly. The following are a few aspects that will need to be added to the current oncology training to keep up with the changing face of oncology.

8.1 Genetics

Owing to the development in the field of genetics and increasing involvement of genetics in prevention and treatment of cancers, it has become utmost important for any oncologist, medical, radiation or surgery to have a basic knowledge of cancer genetics. Any cancer training course would be incomplete without an understanding of genetics in the future.

8.2 Research

Although the current training schedules encourage students to get involved in various research activities, it is necessary to have a dedicated curriculum for protocol development and conducting basic and clinical trials so that cancer treatment can progress in our country to match the standards of the western world.

8.3 Sub-specialization

What seems like an obvious next step of metamorphosis of oncology training to move away from the general oncology training and towards a more site specific, organ-specific cancer training as that would help the students to excel in oncology of one subsite, is not an easy decision. While the organ-specific 'only' training will help the students excel, it will come at the cost of having fewer 'general' oncologists, which is the current demand of the country. As per a report published, India has an oncologist density of 1 for one million population [3] and 1 oncologist for 2000 patients [4]. Hence, continuing to train trainees in general oncology may be the need of the hour, but a site-specific oncology training is the need of a near future.

8.4 Mentor/Mentee Program

Owing to the mental dexterity of the course, it would be useful to include a formal mentor / mentee program in the oncology training as a strong mentor mentee program has shown to improve productivity and student satisfaction [5] and is important for successful professional development [6].

Finally, there is a definite need for harmonization of cancer education and training across the country in order to achieve the ultimate goal of delivering quality cancer care to patients across the country by qualified and appropriately trained personnel.

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